The American Journal of Medicine

EDITORIAL BOARD

The American Journal of Medicine

Editor: ALEXANDER B. GUTMAN, M.D.
Professor of Medicine
COLUMBIA UNIVERSITY COLLEGE OF PHYSICIANS AND SURGEONS, NEW YORK
DIRECTOR, DEPARTMENT OF MEDICINE, THE MOUNT SINAI HOSPITAL, NEW YORK

Assistant Editors: MORTIMER E. BADER, M.D. AND RICHARD A. BADER, M.D.
THE MOUNT SINAI HOSPITAL, NEW YORK

ADVISORY BOARD

DAVID P. BARR, M.D.
Professor Emeritus of Medicine
CORNELL UNIVERSITY MEDICAL COLLEGE
NEW YORK

ARTHUR L. BLOOMFIELD, M.D.
Professor Emeritus of Medicine
SCHOOL OF MEDICINE, STANFORD UNIVERSITY
SAN FRANCISCO

A. MCGEHEE HARVEY, M.D.
Professor of Medicine
JOHNS HOPKINS UNIVERSITY, SCHOOL OF MEDICINE
BALTIMORE

WALTER L. PALMER, M.D.
Professor of Medicine
UNIVERSITY OF CHICAGO, SCHOOL OF MEDICINE
CHICAGO

ASSOCIATE EDITORS

S. HOWARD ARMSTRONG, JR., M.D., *Chicago*
PAUL B. BEESON, M.D., *New Haven*
J. RUSSELL ELKINTON, M.D., *Philadelphia*
PETER H. FORSHAM, M.D., *San Francisco*
ROBERT M. KARK, M.D., *Chicago*
WILLIAM S. MCCANN, M.D., *Rochester, N. Y.*
GEORGE R. MENEELY, M.D., *Nashville*
CARL V. MOORE, M.D., *St. Louis*
JACK D. MYERS, M.D., *Pittsburgh*
ROBERT E. OLSON, M.D., *Pittsburgh*
DEWITT STETTEN, JR., M.D., *Bethesda*
JOHN V. TAGGART, M.D., *New York*
GEORGE W. THORN, M.D., *Boston*

The American Journal of Medicine is published monthly by The American Journal of Medicine, Inc., 11 East 36th Street, New York 16, N. Y. Yearly Subscription, $12.00 U. S. A.; $13.00 Canada; $16.00 Foreign, including Latin-American countries. Single Numbers $2.00; Special and Symposium Numbers $4.00. Second-class postage paid at New York, N. Y. and at additional mailing offices, August, 1959—Volume XXVII, No. 2. *Copyright © 1959, by The American Journal of Medicine, Inc. No part of the contents of this publication may be reproduced or distributed without the express written consent of the publishers.*

MANUSCRIPTS: All manuscripts should be typewritten double space and addressed to the Editorial Office of The American Journal of Medicine, 11 East 36th St., New York 16, N. Y. The top should be indicated on the back of each photograph. *Style for bibliography:* DOE, J. J. Treatment of hypertension. Am. J. Med., 6: 72, 1948.

Change of address must reach us one month preceding month of issue.

ADVERTISING REPRESENTATIVES

New York: Pliny A. Porter, Parker D. Brewer, Howard S. Schultz, Ronald P. Davis
—MUrray Hill 3-2980

Chicago: R. H. Andrew, C. P. Haffner
—FRanklin 2-3861

after the coronary

Peritrate improves blood flow
...with no significant
drop in blood pressure

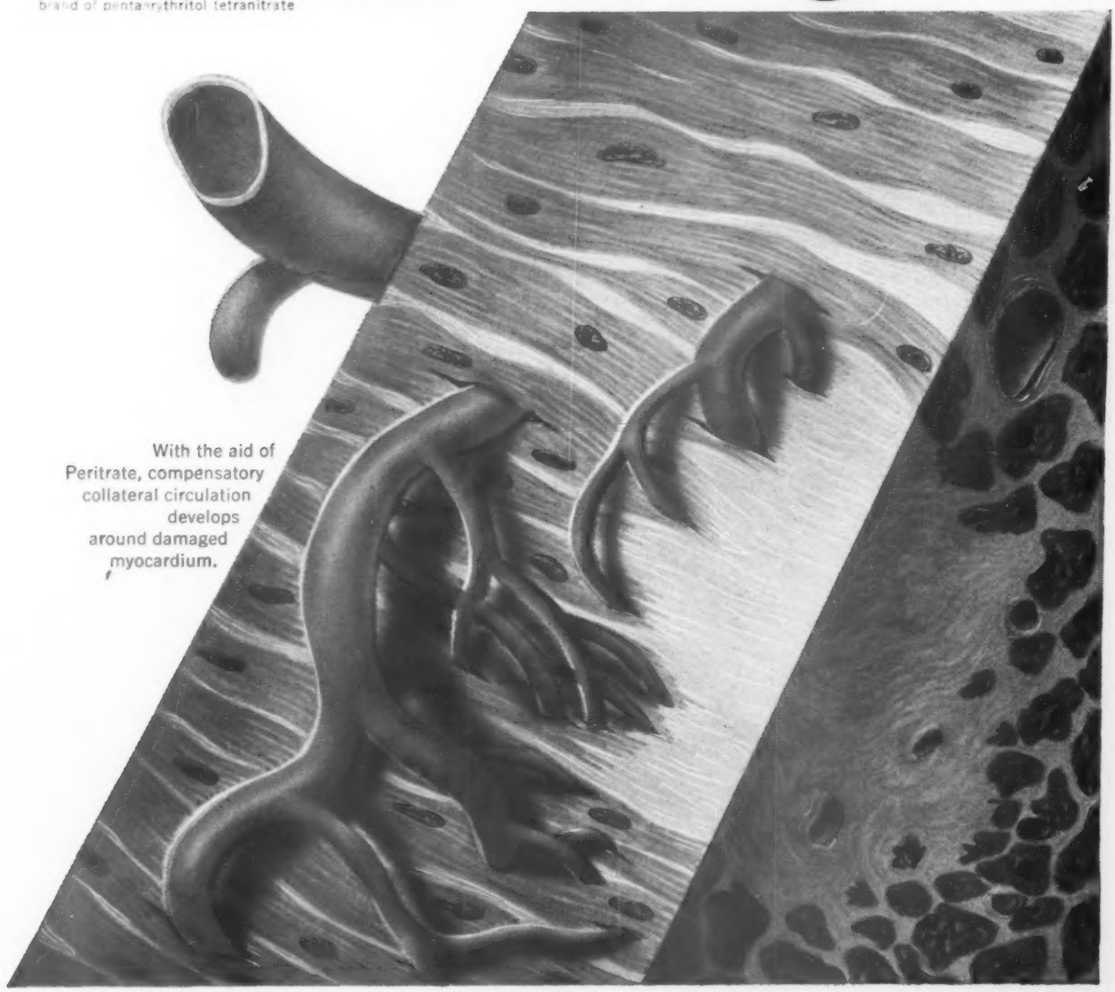
Peritrate aids in the establishment of vital collateral circulation in the postcoronary patient.

Unlike nitroglycerin, Peritrate is a **selective** vasodilator that works almost exclusively on coronary vessels with only minimal peripheral effects. It increases coronary blood supply without significant fall in blood pressure or increase in pulse rate. Prescribe Peritrate 20 mg. q.i.d. for your postcoronary patients.

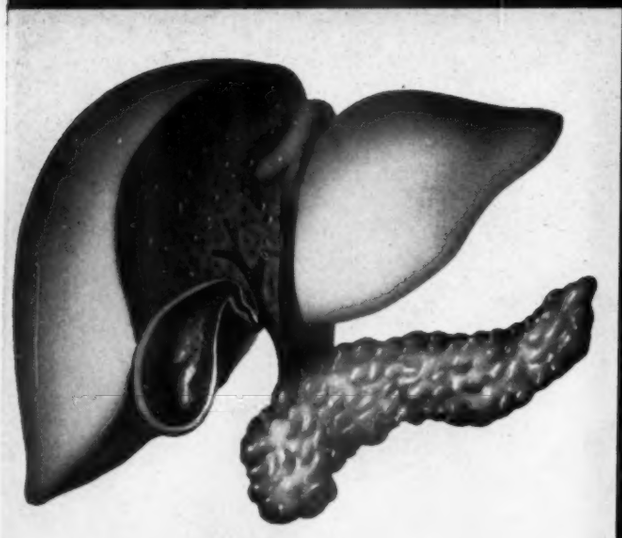
WARNER
CHILCOTT
MORRIS PLAINS, N.J.

Peritrate® 20 mg.

brand of pentaerythritol tetranitrate



With the aid of Peritrate, compensatory collateral circulation develops around damaged myocardium.



why should the urine be tested for sugar in acute cholecystitis?

The high incidence of pancreatic disease associated with pathologic conditions of the biliary tract indicates their close relationship. The appearance of glycosuria in acute cholecystitis points to involvement of the pancreas in the inflammatory process.

Source: Refresher Article: Biliary Tract Diseases, M. Times *85*:1081, 1957.

to help forewarn of pancreatic involvement...
and for reliable urine-sugar testing at any time

color-calibrated CLINITEST® BRAND
Reagent Tablets

"...the most satisfactory method for home and office routine testing...."
GP *16*:121 (Aug.) 1957.

- STANDARDIZED READINGS...familiar blue-to-orange spectrum
- STANDARDIZED "PLUS" SYSTEM...covers entire clinical range
- STANDARDIZED SENSITIVITY...avoids insignificant trace-reaction

consistently reliable results
day after day...
test after test

AMES
COMPANY, INC
Elkhart • Indiana
Toronto • Canada

The American Journal of Medicine

Vol. XXVII AUGUST 1959 No. 2

CONTENTS

Editorial

Cirrhosis in Alcoholics . . . . . CHARLES S. DAVIDSON AND HANS POPPER 193

Clinical Studies

The Effect of a Low Fat Diet on the Serum Lipids in Diabetes and Its Significance in Diabetic Retinopathy . . . . . WILLIAM F. VAN ECK 196

As the author points out, the usual diabetic diet provides liberal amounts of fat and one might well ponder the role that such a high fat diet might play in the development of elevated serum lipid levels and associated vascular changes, notably retinopathy, in diabetic patients. In any event, institution of a very low fat diet (20 gm./day) resulted in a decline in serum lipids and rather striking improvement of diabetic retinopathy, particularly in clearing of exudates. The augmented carbohydrate intake necessary to maintain caloric balance was surprisingly well tolerated, without increase in the insulin requirement, as previously demonstrated with the Kempner rice–fruit regimen.

The Effects of Fasting and Diabetes Mellitus on Myocardial Metabolism in Man WALTER T. GOODALE, ROBERT E. OLSON AND DONALD B. HACKEL 212

In fasting, the arterial blood concentrations of glucose, pyruvate and lactate decline, and the myocardium (which ordinarily extracts these components at a rate dependent upon their concentration in the blood) consequently removes and utilizes less of them than after feeding. Under such circumstances, the myocardium depends largely upon fat for energy production.

Proteins, Lipoproteins and Protein-Bound Carbohydrates in the Serums of Diabetic Patients . . PEDRO EJARQUE, ALEXANDER MARBLE AND ELIZABETH F. TULLER 221

This is a continuing study of alterations in the serum protein fractions, particularly of lipo- and glycoproteins, in diabetic subjects in order to detect changes that might be correlated with the presence of or predisposition to vascular complications. The findings indicate slight but statistically significant abnormalities; an increase in alpha-2 globulins and some decrease in albumin and gamma globulin, particularly in patients with combined nephropathy, retinopathy and neuropathy. The beta lipoproteins tended to be higher, the alpha lipoproteins lower, when diabetic nephropathy was present. An indication of possible qualitative changes in the alpha-2 globulin fraction was noted in patients with the "triopathy" of diabetes, and increase in the protein-bound carbohydrate of this fraction.

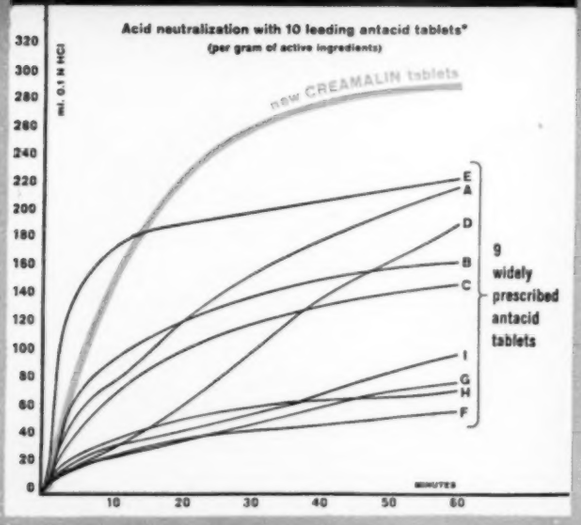
Contents continued on page 5

THE MOST SIGNIFICANT IMPROVEMENT IN ANTACID THERAPY SINCE THE INTRODUCTION OF ALUMINUM HYDROXIDE IN 1929

NEW Creamalin® ANTACID TABLETS

CREAMALIN NEUTRALIZES *MORE* ACID *FASTER*

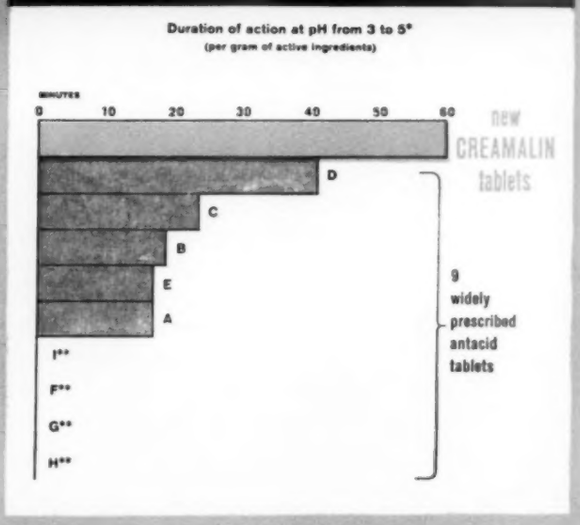
Quicker Relief · Greater Relief



Tablets were powdered and suspended in distilled water in a constant temperature container (37°C) equipped with mechanical stirrer and pH electrodes. Hydrochloric acid was added as needed to maintain pH at 3.5. Volume of acid required was recorded at frequent intervals for one hour.

CREAMALIN NEUTRALIZES *MORE* ACID *LONGER*

More Lasting Relief



*Hinkel, E. T., Jr., Fisher, and Tainter, M. L.: A new highly reactive aluminum hydroxide complex for gastric hyperacidity. To be published.
**pH stayed below 3.

Each Creamalin Antacid Tablet contains 320 mg. specially processed, highly reactive, short polymer dried aluminum hydroxide gel, (stabilized with hexitol), with 75 mg. magnesium hydroxide.

1. *Neutralizes acid faster (quicker relief)*
2. *Neutralizes more acid (greater relief)*
3. *Neutralizes acid longer (more lasting relief)*
4. *No constipation · No acid rebound*
5. *More pleasant to take*

No chalky taste. New CREAMALIN tablets are not chalky, gritty, rough or dry. They are highly palatable, soft, smooth, easy to chew, mint flavored.

Adult Dosage: Gastric hyperacidity—2 to 4 tablets as necessary. Peptic ulcer or gastritis—2 to 4 tablets every two to four hours. Tablets may be chewed, swallowed with water or milk, or allowed to dissolve in the mouth.

Supplied: Bottles of 50, 100, 200 and 1000.

Winthrop LABORATORIES · NEW YORK 18, NEW YORK

CONTENTS continued – August 1959

VOLUME TWENTY-SEVEN NUMBER TWO

Use of I^{131}-Labelled Fat in the Study of Lipid Handling in Patients with Coronary Artery Disease

ROBERT H. SELLER, JONAS BRACHFELD, HERSCHEL SANDBERG AND SAMUEL BELLET 231

The investigators use a recently introduced and rather novel approach to the question of abnormal lipid metabolism in atherosclerosis; namely, measurement of the rate of appearance and/or disappearance of lipoprotein-bound lipid in the blood after ingestion of I^{131}-labelled fat, a method principally used hitherto in the study of malabsorption states. The results indicate significantly higher values in patients who have had myocardial infarction, even though their serum cholesterol, lipid phosphorus and alpha and beta lipoprotein levels may be within normal limits. As the authors point out, the reliability and specificity of this technic for the detection of presumptive atherosclerosis must be further tested but the results are in any event of interest from the point of view of possible abnormalities in the disposition of lipid.

Blood Volume in Patients with Acute Glomerulonephritis As Determined by Radioactive Chromium Tagged Red Cells

SEYMOUR EISENBERG WITH THE TECHNICAL ASSISTANCE OF MARY SUE MCCALL AND SUE KELLER 241

This study, by what would seem to be an impeccable technic, appears to resolve a question which has been batted back and forth for a long time: the pathogenesis of the congestive phenomena encountered in acute glomerulonephritis. It is shown that, at least in the edematous phase of illness, there is a substantial increase in plasma volume which, unlike intrinsic congestive heart failure, is not associated with a commensurate increase in red cell mass. While overlapping phenomena doubtless occur, the hypervolemia of acute glomerulonephritis is therefore not primarily due to low output cardiac failure but is essentially an example of non-cardiac circulatory congestion. The accompanying "anemia" is attributable to dilution.

Hereditary Aspects of Gastric Secretory Function. Race and ABO Blood Groups in Relationship to Acid and Pepsin Production . . . . . MAURICE L. SIEVERS 246

This is an interesting study which demonstrates a (statistically) significantly greater incidence of impairment of gastric acid and pepsin secretion in blood group A than in O subjects. It would thus appear that functional gastric atrophy, presumably by reason of heritable factors, occurs more frequently in patients with blood group A and, conversely, less frequently in patients with blood group O. This at once suggests a possible relationship with the well known demonstrations that pernicious anemia and gastric malignancy occur with significantly greater frequency in subjects with blood group A, whereas duodenal ulcer is more common in subjects with blood group O.

Contents continued on page 7

why ? ? ? ?

WIGRAINE®
FOR MIGRAINE

HERE'S WHY: Wigraine is complete therapy for migraine. Combats all phases of the migraine attack: headache, nausea and vomiting, residual occipital muscle pain. Wigraine is uncoated; disintegrates in seconds, brings fast relief. Wigraine is swallowed easily; no taste or aftertaste problem. In tablets or suppositories, both containing the following time-tested formula:

Ergotamine tartrate	1 mg.
Caffeine	100 mg.
l-Belladonna Alkaloids*	0.1 mg.
Acetophenetidin	130 mg.

*87.5% hyoscyamine and
12.5% atropine as sulfates

for samples write:

Medical Department

Organon Inc., Orange, New Jersey

CONTENTS continued—August 1959

VOLUME TWENTY-SEVEN NUMBER TWO

Review

Anatomy of Body Water and Electrolytes . . . . I. S. EDELMAN AND J. LEIBMAN 256

The authors begin with a consideration of the changing concepts of compartmentalization of body water and electrolytes, stressing the difficulties in inflexible separations, particularly of the extracellular phases. Nevertheless, four main subdivisions can be usefully defined, namely, plasma; interstitial and lymph fluid; dense connective tissue, cartilage and bone; and transcellular fluids. The distribution of body water, sodium, potassium and chloride is then discussed within this framework, taking into account the results of the varied technics which have been employed for the purpose, discordant as they may be. Out of the welter of data comes a meaningful design which resolves some of the confusion of the past—altogether an impressive achievement, well worth study.

Seminar on Mycotic Infections

The Course and Prognosis of Histoplasmosis
HARRY RUBIN, MICHAEL L. FURCOLOW, J. LEWIS YATES AND CHARLES A. BRASHER 278

This analysis of 123 cases of histoplasmosis considers three categories of histoplasmosis infection: acute pulmonary (eight cases), chronic pulmonary (ninety cases) and disseminated (twenty-five cases). The clinical and laboratory manifestations of each category are described. Of interest is the point that prolonged follow-up reveals progression of pulmonary involvement in chronic pulmonary histoplasmosis (still all too frequently confused with tuberculosis) and that the disseminated form of the disease is not invariably fatal, even without treatment, as commonly believed. This does not, of course, diminish the importance of therapy, notably amphotericin B.

Clinicopathologic Conference

Hypertension, Renal Disease and Potassium Wasting 289

Clinicopathologic Conference (Washington University School of Medicine).

Research Society Abstracts

Southern Society for Clinical Research—Abstracts of Papers Presented at the Thirteenth Annual Meeting, New Orleans, Louisiana, January 23, 1959 . . . 304

Contents continued on page 9

KENACORT

SQUIBB TRIAMCINOLONE

for all your patients starting on corticoids

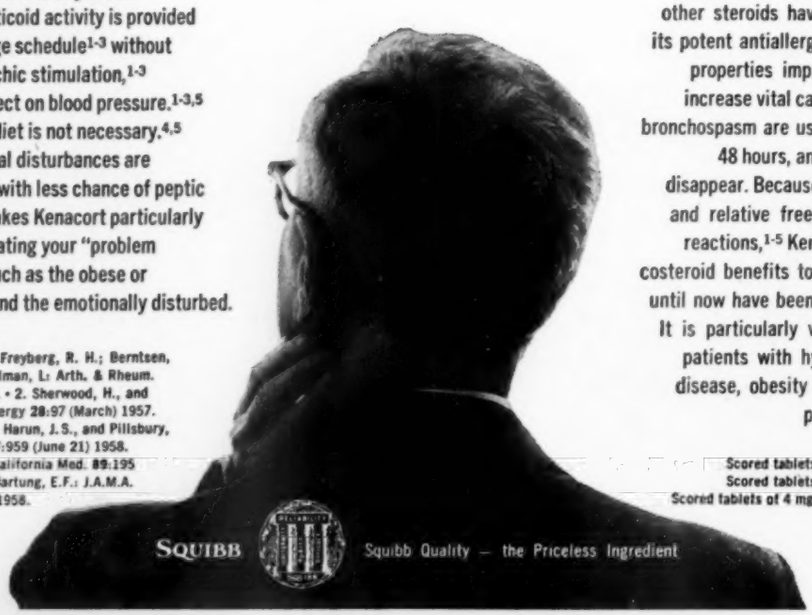
Kenacort safely starts your patients off right — with all the benefits of systemic corticosteroid therapy and few side effects to worry about. Increased corticoid activity is provided on a low dosage schedule[1-3] without edema,[1-4] psychic stimulation,[1-3] or adverse effect on blood pressure.[1-3,5] A low sodium diet is not necessary.[4,5] Gastrointestinal disturbances are negligible[2,4,5] with less chance of peptic ulcer.[4] This makes Kenacort particularly valuable in treating your "problem patients" — such as the obese or hypertensive and the emotionally disturbed.

for all your allergic patients requiring corticoids

Kenacort, in treating your allergic patients, has proved effective where other steroids have failed. In asthma, its potent antiallergic and inflammatory properties improve ventilation and increase vital capacity.[2] Dyspnea and bronchospasm are usually relieved within 48 hours, and sibilant râles often disappear. Because of its low dosage[1-3] and relative freedom from untoward reactions,[1-5] Kenacort provides corticosteroid benefits to many patients who until now have been difficult to control. It is particularly valuable for allergic patients with hypertension, cardiac disease, obesity and those prone to psychic disturbances.

REFERENCES: • 1. Freyberg, R. H.; Berntsen, C. A., Jr., and Hellman, L.: Arth. & Rheum. 1:215 (June) 1958. • 2. Sherwood, H., and Cooke, R. A.: J. Allergy 28:97 (March) 1957. • 3. Shelley, W. B.; Harun, J. S., and Pillsbury, D. M.: J.A.M.A. 167:959 (June 21) 1958. • 4. Dubois, E.L.: California Med. 89:195 (Sept.) 1958. • 5. Hartung, E.F.: J.A.M.A. 167:973 (June 21) 1958.

SUPPLIED:
Scored tablets of 1 mg. — Bottles of 50
Scored tablets of 2 mg. — Bottles of 50
Scored tablets of 4 mg. — Bottles of 30 and 100



SQUIBB

Squibb Quality — the Priceless Ingredient

"KENACORT" ® IS A SQUIBB TRADEMARK

CONTENTS continued–August 1959

VOLUME TWENTY-SEVEN NUMBER TWO

Case Reports

Thrombotic Thrombocytopenic Purpura of Long Duration
SEAMUS F. CAHALANE AND ROBERT C. HORN, JR. 333

Since really specific clinical, laboratory and even pathologic criteria for the diagnosis of thrombotic thrombocytopenic purpura are still lacking, it is difficult to define this interesting disorder in pathognomonic terms. The present report cites a case, and others from the literature, indicating that, as seems likely, the disease may run a more protracted course than the fulminant one of the classic descriptions.

Polyneuritis with Albuminocytologic Dissociation in the Spinal Fluid in Systemic Lupus Erythematosus. Report of a Case, with Review of Pertinent Literature
MARTIN GOLDBERG AND HATAI CHITANONDH 342

An instructive, well studied case.

Diagnosis of Whipple's Disease by Peripheral Lymph Node Biopsy. Report of a Case
W. CROCKETT CHEARS, JR., ALBERT G. SMITH AND JULIAN M. RUFFIN 351

The usefulness of biopsy and PAS staining of likely peripheral nodes in establishing the diagnosis of Whipple's disease would seem to deserve additional emphasis.

Crystalline Glomerular Deposits in Multiple Myeloma . . . G. WILLIAM SICKEL 354

An unusual observation.

Advertising Index on Page 135

Change of address must reach us one month preceding month of issue.

because it "most closely approaches the 'ideal anticoagulant,'"[1]

COUMADIN has become widely accepted as the anticoagulant of choice[1-3]

"most of the drawbacks of Dicumarol have been overcome [with COUMADIN] ... It is my firm belief that in time it will replace Dicumarol on the basis of its performance over a wide variety of conditions..."[2]

COUMADIN®

ORAL
I.V. or I.M.

SODIUM

IN MYOCARDIAL INFARCTION AND OTHER THROMBOEMBOLIC DISORDERS

After more than five years' clinical experience, it has been concluded: "In my opinion, Warfarin sodium [COUMADIN] is the best anticoagulant available today."[3]

COUMADIN CONSISTENTLY PROVIDES

rapid and sustained effect with low dosage • high predictability • ease of control for long periods • low incidence of "escape" • equal effectiveness by oral or parenteral routes • reduced need for frequent prothrombin time determinations after initial dosage adjustment • ready reversibility with vitamin K_1

Complete Information and Reprints on Request

Endo®
ENDO LABORATORIES
Richmond Hill 18, New York

TABLETS
For oral administration—2 mg., lavender, scored; 5 mg., peach, scored; 10 mg., white, scored; 25 mg., red, scored.

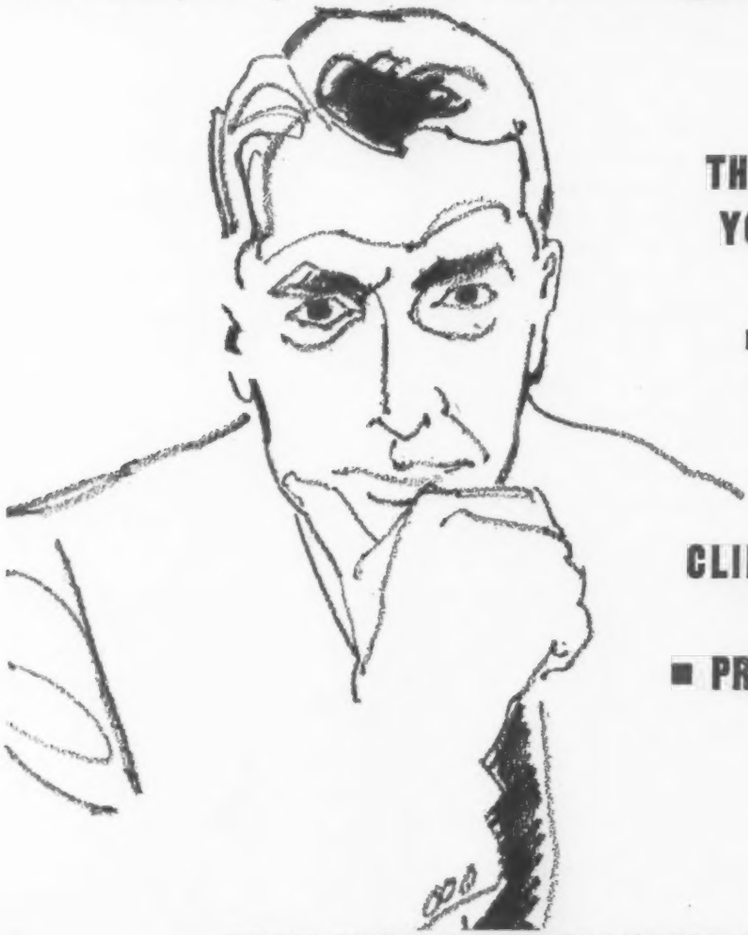
INJECTION
For parenteral administration—Single Injection Units, consisting of one vial, 75 mg., and one 3-cc. ampul Water for Injection.

AVERAGE DOSE
Initial, 50 mg. *Maintenance*, 5-10 mg. daily, as indicated by prothrombin time determinations.

COUMADIN (warfarin) Sodium—manufactured under license from the Wisconsin Alumni Research Foundation—*developed for clinical use by Endo.*

References: 1. Baer, S., et al.: J.A.M.A. 167:704, 1958. 2. Link, K. P.: Circulation 19:97, 1959. 3. Meyer, O. O.: Postgrad. Med. 24:110, 1958.

doctor, if you are not completely satisfied



...IF THE ANTIHISTAMINES YOU ARE NOW USING:

- **ARE INEFFECTIVE IN SOME PATIENTS**
- **ARE LIMITED IN CLINICAL APPLICATION**
- **PRODUCE UNDESIRABLE SIDE EFFECTS**

THEN YOUR NEXT ALLERGIC PATIENT MAY NEED

New TOTAL ACTION "THERUHISTIN" FORTE®

Brand of Isothipendyl hydrochloride

Sustained Action Tablet for daylong antiallergic effect

A new antihistaminic/anticholinergic/antiserotonin agent of "high potency and efficiency"[1] **sustained relief** in an average of over 90 per cent of 1209 cases of various allergic diseases[1-3] ■ **strikingly free of side effects** ■ **has been used successfully in all varieties of allergy...** of considerable value in bronchial asthma

Also available: "THERUHISTIN" Syrup. Potency recently increased from 2 to 4 mg. per 5 cc. (1 tsp.). *Usual dosage for children:* ½ to 1 tsp. two to four times daily depending on age.

Usual Dosage: One tablet morning and evening.

Supplied: No. 737—24 mg. Sustained Action Tablets, bottles of 100 and 1,000.

1. Committee on New and Unused Therapeutics, Am. Coll. Allergists: Ann. Allergy 16:237 (May-June) 1958. 2. Spielman, A. D.: Ann. Allergy 16:242 (May-June) 1958. 3. Spielman, A. D.: New York J. Med. 57:3329 (Oct. 15) 1957.

Ayerst®

AYERST LABORATORIES
New York 16, N. Y.
Montreal, Canada

5940

FOR THE NEW "MATURITY-ONSET" DIABETIC CONSIDER DIABINESE® FIRST

brand of chlorpropamide

tablets / once-a-day dosage

for smoother, lower-cost oral antidiabetic control

The specific pharmacologic properties of DIABINESE—high activity, freedom from metabolic degradation, and gradual excretion—permit (1) prompt lowering of elevated blood sugar levels *without a "loading" dose*, and (2) smooth, sustained maintenance "devoid of... marked blood sugar fluctuations"[1] on convenient, lower-cost, once-a-day dosage. This is the consensus of extensive clinical literature.[1-11] Widespread use of DIABINESE since its introduction has confirmed the low incidence of side effects reported by the original investigators.

Thus, DIABINESE merits *first* consideration for any diabetic presently receiving or potentially better managed with oral therapy—including many diabetics for whom previous oral agents have proved ineffective.

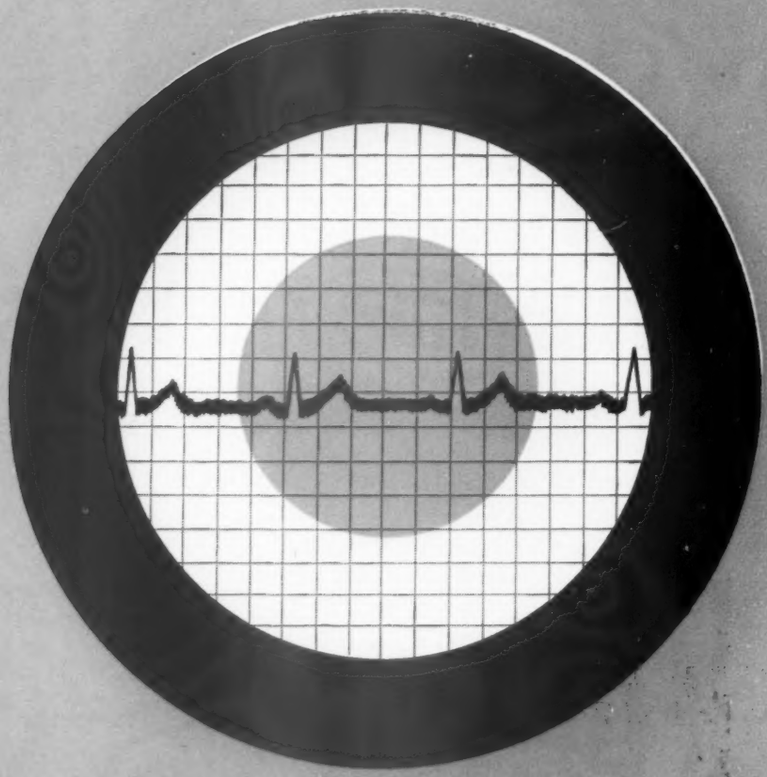
Supplied: **Tablets, white, scored 250 mg., bottles of 60 and 250; 100 mg., bottles of 100.**

Pfizer *Science for the world's well-being*

PFIZER LABORATORIES, Brooklyn 6, New York
Division, Chas. Pfizer & Co., Inc.

1. Greenhouse, B.: Ann. New York Acad. Sc. 74:643, 1959. 2. Dobson, H., et al.: Ibid., p. 940. 3. Forsham, P. H.; Magid, G. J., and Dorosin, D. E.: Ibid., p. 672. 4. Beaser, S. B.: Ibid., p. 701; New England J. Med. 259:573, 1958. 5. Blöch, J., and Lenhardt, A.: Ann. New York Acad. Sc. 74:954, 1959. 6. O'Driscoll, B. J.: Lancet 2:749, 1958. 7. Hadley, W. B.; Khachadurian, A., and Marble, A.: Ann. New York Acad. Sc. 74:621, 1959. 8. Duncan, G. G.; Schless, G. L., and Demeshkieh, M. M. A.: Ibid., p. 717. 9. Handelsman, M. B.; Levitt, L., and Calabretta, M. F.: Ibid., p. 632. 10. Hills, A. G., and Abelove, W. A.: Ibid., p. 845. 11. Drey, N. W., et al.: Ibid., p. 962.

for easy
elimination
in cardiovascular
patients



TARGET ACTION specifically on the large bowel

DORBANE

(1,8-dihydroxyanthraquinone)

selective peristaltic stimulant

▪ smooth, overnight action ▪ no griping ▪ well tolerated, non-habituating

Available in 75 mg. scored tablets and suspension.

WHERE STOOL SOFTENING IS ALSO INDICATED

DORBANTYL FORTE

(Dorbane, 50 mg. + dioctyl sodium sulfosuccinate, 100 mg.)*

Double-strength capsules for maximum economy and convenience.

DORBANTYL®

(Dorbane, 25 mg. + dioctyl sodium sulfosuccinate, 50 mg.)*

For lower dosage and in children.

Available in capsules and suspension.

***In proportions proved optimal by clinical trial in over 550 cases.**

(Marks, M. M.: Clin. Med. 4:151, 1957.)

Schenlabs

SCHENLABS PHARMACEUTICALS, INC., NEW YORK 1, N. Y.

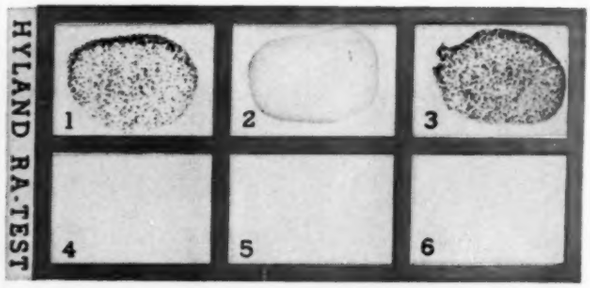
Manufacturers of NEUTRAPEN® for penicillin reactions.

®TRADEMARKS REG. U. S. PAT. OFF. DORBANTYL FORMULA PATENTED 55454

HYLAND RA-TEST
A FAST, SIMPLE, RELIABLE SCREENING TEST FOR RHEUMATOID ARTHRITIS

a rapid slide modification of the latex fixation test

RA-TEST®



EASY TO PERFORM—just mix separate drops of Latex-Globulin Reagent with: (1) patient's diluted serum, (2) Negative Control Serum, and (3) Positive Control Serum on divided areas of slide.

EASY TO READ—positive reactions (indicating presence of rheumatoid factor) are clearly visible to the naked eye in a few seconds. Negative tests remain smooth, with no visible clumping.

SUPPLIED—in compact kits containing 5 cc. Latex-Globulin Reagent, 2 cc. Positive Control Serum, 2 cc. Negative Control Serum, 100 cc. Glycine-Saline Buffer Diluent, and divided glass slide. Each kit sufficient for at least 100 tests. Test components are also available separately.

HYLAND LABORATORIES
Los Angeles 39, California · Yonkers, New York

HYLAND

Of course, women like "Premarin"®

THERAPY for the menopause syndrome should relieve not only the psychic instability attendant the condition, but the vasomotor instability of estrogen decline as well. Though they would have a hard time explaining it in such medical terms, this is the reason women like "Premarin."

The patient isn't alone in her devotion to this natural estrogen. Doctors, husbands, and family all like what it does for the patient, the wife, and the homemaker.

When, because of the menopause, the psyche needs nursing – "Premarin" nurses. When hot flushes need suppressing, "Premarin" suppresses. In short, when you want to treat the whole menopause, (and how else is it to be treated?), let your choice be "Premarin," a complete natural estrogen complex.

"Premarin," conjugated estrogens (equine), is available as tablets and liquid, and also in combination with meprobamate or methyltestosterone.

Ayerst Laboratories • New York 16, N.Y.
Montreal, Canada

Ayerst®

5854

NOW—YOU CAN GET THE UNSURPASSED ADVANTAGES OF ARISTOCORT IN SALICYLATE COMBINATION Arist

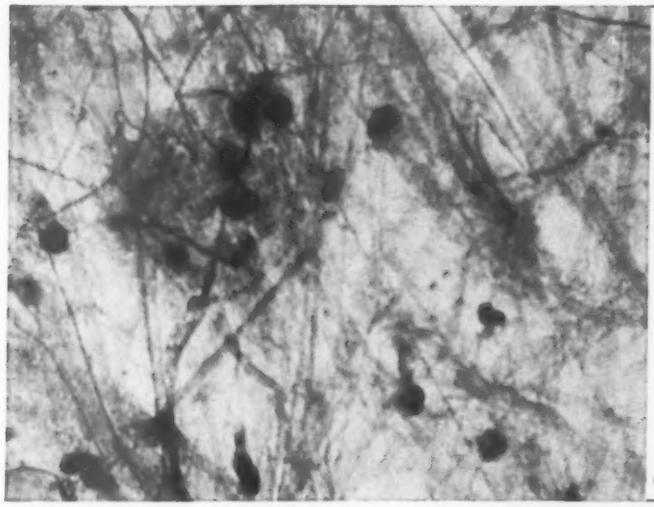
Aristogesic combines the *anti-inflammatory* effects of Aristocort® Triamcinolone with the *analgesic* action of a most potent salicylate. This means that the dosage of each is *substantially lower* than that ordinarily required for each agent alone. With Aristogesic the physician has exceptionally wide latitude in adjusting the dosage to the lowest effective level.

The possibility of gastric distress from either salicylamide or corticosteroid is minimized because of lower dosage required. This is further reduced by the buffer action of aluminum hydroxide. And the ascorbic acid helps meet the increased need for this vitamin in stress conditions. Because of the low dosage, side effects with Aristogesic have been relatively infrequent and minor in nature. However, more serious side effects have traditionally been observed on all corticosteroid therapy. Patients on long-term Aristogesic therapy should, therefore, be observed carefully.

ogesic*

Steroid–Analgesic Compound LEDERLE

for relief of *chronic*–but *less severe* pain of rheumatic origin



Indications: Mild cases of rheumatoid arthritis, tenosynovitis, synovitis, bursitis, mild spondylitis, myositis, fibrositis, neuritis and certain muscular strains.

Dosage: Average initial dosage: 2 capsules 3 or 4 times daily. Maintenance dosage to be adjusted according to response.

Each Aristogesic Capsule contains:

ARISTOCORT® Triamcinolone	0.5 mg.
Salicylamide	325 mg.
Aluminum Hydroxide	75 mg.
Ascorbic Acid	20 mg.

Supply: Bottles of 100.

Collagen tissue (x250)

*TRADEMARK

Lederle

LEDERLE LABORATORIES, A Division of AMERICAN CYANAMID COMPANY, Pearl River, New York

in oral penicillin therapy

the speed of action you want

the reliability you need

Penicillin, still the most frequently prescribed antibiotic, assumes new reliability in the form of PEN·VEE K. Tablet or Liquid PEN·VEE K may be prescribed for all infections responsive to oral penicillin . . . *including many usually treated with parenteral penicillin.*

The speed of action and reliability of oral potassium penicillin V have been dramatically demonstrated by recent studies[1,2] in which 107 subjects were each given 400,000 units of the antibiotic. Appreciable penicillin levels were consistently produced within 15 minutes; peak levels within one-half hour. Penicillin levels still persisted in all subjects at two hours, and in 93 per cent of subjects at four hours.

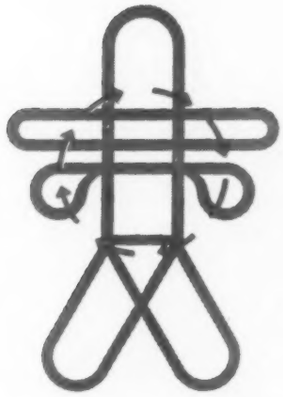
1. Peck, F.B., Jr., and Griffith, R.S.: Antibiotics Annual 1957-1958, Medical Encyclopedia, Inc., p. 1004. 2. Wright, W.W., and Welch, H.: Antibiotic Med. *5*:139 (Feb.) 1958.

PEN·VEE® K

Liquid: Penicillin V Potassium for Oral Solution;
Tablets: Penicillin V Potassium, Wyeth

Wyeth®
Philadelphia 1, Pa.

SUPPLIED: *Liquid*: raspberry-flavored, 125 mg. (200,000 units) per 5-cc. teaspoonful; peach-flavored, 250 mg. (400,000 units) per 5-cc. teaspoonful. Both supplied as vials of powder to make 40 cc. *Tablets*: 125 mg. (200,000 units) and 250 mg. (400,000 units) in vials of 36.



thrombophlebitis and pulmonary embolism

ACTASE
TRADEMARK

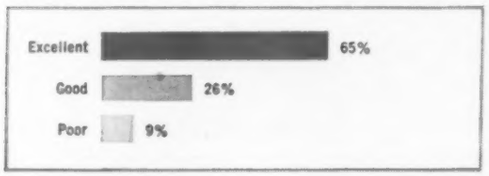
Fibrinolysin (Human)

DISSOLVES INTRAVASCULAR CLOTS

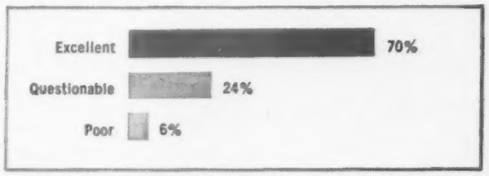
ACTASE is a highly purified preparation of the naturally occurring[1] enzyme fibrinolysin. Its ability to liquefy intravascular clots[2] and restore patency to obstructed vessels has been clinically demonstrated.[3,4]

PROVEN CLINICALLY

ACTASE IN VENOUS THROMBOSIS (171 PATIENTS)*



ACTASE IN PULMONARY EMBOLISM (33 PATIENTS)*



*Adapted from Singher, H. O., and Chapple, R. V.[5]

SAFETY—In recommended dosage ACTASE does not interfere with blood coagulation.

ADMINISTRATION—ACTASE is administered by intravenous infusion over a 2-hour period. ACTASE is most effective when given soon after the formation of the clot. The concomitant use of anticoagulants is recommended. A temperature rise (1° to 5.2° F.) may occur with ACTASE. This may be ameliorated with conventional antipyretic therapy.

CONTRAINDICATIONS: Hemorrhagic diathesis; major liver dysfunction; hypofibrinogenemia.

SUPPLIED: Vials of 50,000 Fibrinolytic Units.

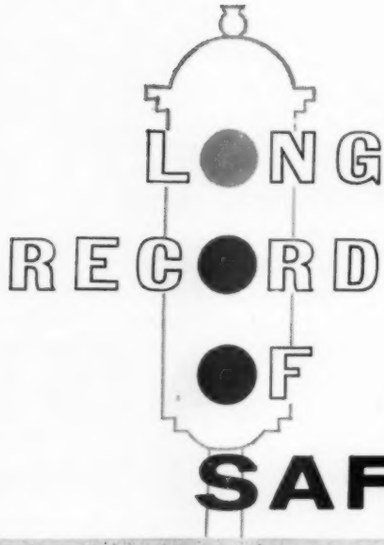
Complete information available on request.

REFERENCES: (1) Astrup, T.: Lancet *2*:565 (Sept. 15) 1956. (2) Clifton, E. E.: Ann. New York Acad. Sc. *68*:209 (Aug. 30) 1957. (3) Clifton, E. E.: J. Am. Geriatrics Soc. *6*:118, 1958. (4) Sussman, B. J., and Fitch, T. S. P.: J.A.M.A. *167*:1705 (Aug. 2) 1958. (5) Singher, H. O., and Chapple, R. V.: Clin. Med. *6*:439 (March) 1959.

Ortho

ORTHO PHARMACEUTICAL CORPORATION
RARITAN, NEW JERSEY

09159



SAFETY

WITH

HP* ACTHAR® GEL

*Highly Purified

SAFETY is not a matter of short-term trials, but determined by years of experience. A record of more than nine years of continuous treatment in a closely supervised group of patients without occurrence of serious side effects is an assurance of safety.

EXPERIENCE is another solid basis for the assurance of safety. HP*ACTHAR *Gel* has the most extensive clinical and experimental background, with the longest history of use in practice.

HIGH PURITY contributes to the safety of HP*ACTHAR *Gel*. Because of this purity, HP*ACTHAR *Gel* is the only ACTH which may be given subcutaneously, intramuscularly, or intravenously (by infusion).

SUPPLIED: 5 cc. vials of 20, 40, 80 U.S.P. Units per cc. Also in a disposable syringe form, in a potency of 40 U.S.P. Units per cc.

ARMOUR

HP*ACTHAR *Gel* is the Armour Pharmaceutical Company brand of purified repository corticotropin (ACTH).

ARMOUR PHARMACEUTICAL COMPANY

A Leader in Biochemical Research

KANKAKEE, ILLINOIS

In skeletal-muscle disabilities . . .

Curbs spasm, relieves rigidity, and relaxes psychic tension

Of all muscle relaxants in current use, only meprobamate is supported by hundreds of published clinical studies that demonstrate relaxing action on both the brain and the skeletal musculature. EQUANIL reduces muscular spasm and tension, aids in the restoration of mobility, speeds rehabilitation, lessens the emotional overlay.

Prescribe it in spasm or tension secondary to: sprains, strains, contractures, fibrositis, myositis, low-back syndrome, frozen shoulder, cervical-rib syndrome, herniated intervertebral disk, wryneck, rheumatoid arthritis, rheumatoid or traumatic spondylitis, certain neuromuscular disorders.

Equanil®

Meprobamate, Wyeth

Wyeth® Philadelphia 1, Pa.

when oral tetracycline therapy is impractical—

AND SPEED COUNTS MOST

Sumycin Intramuscular provides rapid, sustained antimicrobial activity, when coma, shock, fulminating infection or postoperative complications hamper administration of Sumycin in the oral form. Concentrations in the blood and tissues reach peak levels for immediate control of tetracycline-sensitive organisms in a broad range of infections.

For immediate therapeutic response — Sumycin Intramuscular with Xylocaine.* Single dose vials containing tetracycline phosphate complex (equivalent to 250 mg. tetracycline HCl), and single dose vials containing tetracycline phosphate complex (equivalent to 100 mg. tetracycline HCl).

SUMYCIN

SQUIBB CRYSTALLINE TETRACYCLINE PHOSPHATE COMPLEX

INTRAMUSCULAR

WITH XYLOCAINE*

	Flexible dosage forms	Tetracycline HCl equivalent (mg.)	Packaging
FOR ORAL THERAPY	Capsules (per capsule)	250 mg.	Bottles of 16 and 100
	Half Strength Capsules (per capsule)	125 mg.	Bottles of 16 and 100
	Syrup (per 5 cc. teaspoonful)	125 mg.	60 cc. bottle
	Aqueous Drops (per cc.)	100 mg.	10 cc. bottle with 'FLEXIDOSE' dropper

SQUIBB

Squibb Quality—the Priceless Ingredient

SUMYCIN® AND FLEXIDOSE' ARE SQUIBB TRADEMARKS *T. M.® ASTRA PHARMACEUTICAL PRODUCTS, INC. FOR LIDOCAINE

Thorazine*

(chlorpromazine, S.K.F.)

one of the fundamental drugs in medicine

After five years of clinical use, 'Thorazine' continues to be recognized as an exceptionally effective therapeutic agent in nearly all fields of medicine. Its value is due to three fundamental properties:

- capacity to alleviate anxiety, tension and agitation without dulling mental acuity
- profound antiemetic effect
- ability to potentiate narcotics and sedatives

Available: Tablets, Spansule* sustained release capsules, Ampuls, Multiple dose vials, Syrup and Suppositories.

SKF Smith Kline & French Laboratories

*T.M. Reg. U.S. Pat. Off.

in urticaria and pruritus

VISTARIL® provides:

hydroxyzine pamoate

SPECIFIC

ANTIHISTAMINIC

EFFECT

in the treatment of a variety of skin disorders commonly seen in your practice.

"While some of the tranquilizers are only partially effective as far as antiallergic activities are concerned . . . [hydroxyzine] has been found, by comparison, to be the most potent thus far . . . "[2]

"The most striking results were seen in those patients with chronic urticaria of undetermined etiology."[1]

. . . reduces—erythema, excoriation, and extent of lesions.[1-4]

PSYCHOTHERAPEUTIC

POTENCY

for effective relief of tension and anxiety.[1-4]

Recommended Oral Dosage: 50 mg. q.i.d. initially; increase or decrease according to individual response.

Supplied as: Vistaril Capsules—25 mg., 50 mg. and 100 mg.

Vistaril Parenteral Solution—10 cc. vials and 2 cc. Steraject® Cartridges, each cc. contains 25 mg. hydroxyzine (as the HCl).

More than a tranquilizer

Pfizer *Science for the world's well-being*

PFIZER LABORATORIES
Division, Chas. Pfizer & Co., Inc.
Brooklyn 6, New York

References: 1. Feinberg, A. R., et al.: J. Allergy *29*:358 (July) 1958. 2. Eisenberg, B. C.: Clin. Med. *5*:897-904 (July) 1958. 3. Robinson, H. M., Jr., et al.: J.A.M.A. *161*:604-606 (June 16) 1956. 4. Robinson, H. M., Jr., et al.: South. M. J. *50*:1282 (Oct.) 1957.

relief from the suffering and
mental anguish of

cancer

THORAZINE* (chlorpromazine, S.K.F.)

one of the fundamental drugs in medicine

Smith Kline & French Laboratories

*T.M. Reg. U.S. Pat. Off.

open the airway with new 'FEDRAZIL'® TABLETS

when colds or allergies
congest the respiratory tract

- decongest the **entire** respiratory tract mucosa
- dilate the bronchi
- provide potent **anti-allergic** action

DOSAGE: *Adults and Children over 8 years*—
1 or 2 tablets, three times daily.
Children 2-8 years—1 tablet daily, or as required.

Each tablet contains: 'Sudafed'® brand Pseudoephedrine Hydrochloride, 30 mg.; 'Perazil'® brand Chlorcyclizine Hydrochloride, 25 mg. Bottles of 100, sugar-coated.

BURROUGHS WELLCOME & CO. (U.S.A.) INC., Tuckahoe, New York

in

childbirth

THORAZINE®

brand of chlorpromazine

'Thorazine' as adjunctive therapy has four advantages:

1. reduces suffering
2. minimizes risk of respiratory depression
3. controls nausea and vomiting
4. relieves apprehension and agitation

SKF Smith Kline & French Laboratories

2 *exclusive advantages in quinidine therapy*[1,2] *to control* **cardiac arrhythmias**

QUINAGLUTE®
DURA-TAB S.M.®

the only oral Sustained Medication* Quinidine Gluconate (5 gr.)

b.i.d. dosage (every 12 hours)

Each dose of **Quinaglute Dura-Tab S.M.** maintains uniform plasma levels up to 12 hours.
No night dosage needed.
No valleys where arrhythmias tend to recur.[1]

a well tolerated quinidine

Only **Quinaglute Dura-Tab S.M.** provides quinidine gluconate for oral use. Ten times as soluble as quinidine sulfate, the gluconate is better tolerated by the gastrointestinal tract.

An unexcelled quinidine in premature contractions auricular tachycardia flutter, fibrillation

REFER TO PDR PAGE 867

Dosage: for **conversion** of auricular fibrillation to normal sinus rhythm, in most cases, 2 Quinaglute Dura-Tab S.M. tablets 3 to 4 times a day, for 2 to 3 days; longer periods are required in some patients . . . for **maintenance** 1 to 2 tablets every 10 to 12 hours. Bottles of 30, 100 and 250.

1. Bellet, S.: Finkelstein, D., and Gilmore, H.: A.M.A. Archives Int. Med. 100:750, 1957.
2. Bellet, S.: Amer. Heart J. 56:479, 1958.

Samples and complete literature available from **WYNN PHARMACAL CORPORATION**
5119 West Stiles Street, Philadelphia 31, Pa.

Now also available... INJECTABLE QUINAGLUTE
10 cc. Multiple Dose Vials, 0.08 Gm. Quinidine Gluconate per cc.

* U. S. PATENT 2,895,881

Quiescence needed

in medical illness in surgery in obstetrics

One of the most versatile agents known, PHENERGAN helps smooth the management of patients under medical, surgical, or obstetrical stress without depressing vital functions. For many areas of general and specialty practice, PHENERGAN has these actions for these benefits:

Sedation: Relieves fear, promotes sleep, encourages cooperation, reduces postoperative excitement—widely useful in obstetrical and surgical sedation.

Antiemesis: Prevents and controls nausea and vomiting associated with motion sickness, surgery, pregnancy, or reflex mechanisms.

Antiallergy: Gives potent and prolonged antihistaminic control of many allergic reactions.

Drug potentiation: Reduces dose requirements of anesthetics, barbiturates, and narcotic analgesics—an important aid to perisurgical and obstetrical management.

PHENERGAN®

HYDROCHLORIDE

Promethazine Hydrochloride, Wyeth

INJECTION • TABLETS • SYRUP • SUPPOSITORIES

Wyeth®
Philadelphia 1, Pa.

Comprehensive literature supplied on request

How many patients today complained about pain?

non-narcotic—pain relief equivalent to that of codeine

well tolerated in both acute and prolonged use

wide range of indications—general practice and the specialties

analgesia plus anti-inflammatory action

Supplied: Tablets, bottles of 48. Each tablet contains 75 mg. of ethoheptazine citrate and 325 mg. (5 grains) of acetylsalicylic acid.

remember

PAIZactirin®

Ethoheptazine Citrate with Acetylsalicylic Acid, Wyeth

Wyeth®
Philadelphia 1, Pa.

now "a fundamentally new therapeutic approach"[1]

in fungous infections of skin, hair and nails

oral **fulvicin*** griseofulvin

Schering

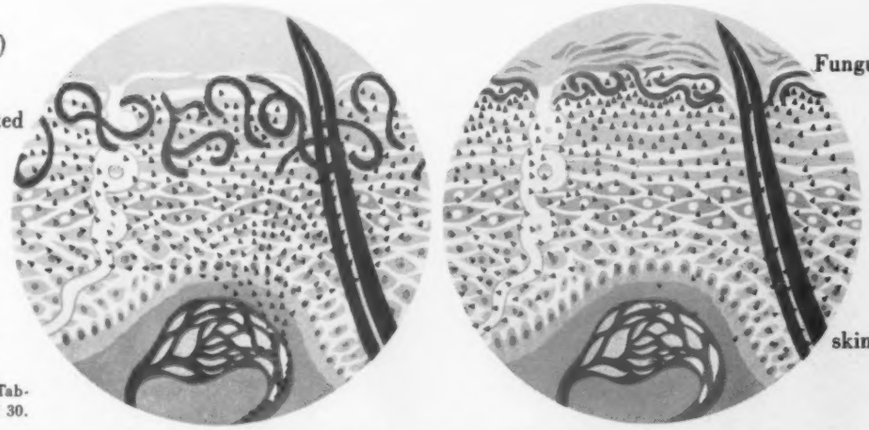
FIRST EFFECTIVE PENETRATION OF KERATIN—FROM THE INSIDE

Pathogenic fungi invade and proliferate in the stratum corneum (and also in keratinized part of nails and hair), where they are usually inaccessible to treatment from the outside by topical antifungal agents, even with the aid of keratolytics.

Following oral administration, FULVICIN is absorbed and incorporated in newly growing dermal cells. As these cells approach the surface and become keratinized, they retain sufficient amounts of FULVICIN to provide fungistasis. FULVICIN has also been identified in hair shafts in fungistatic concentrations.[2]

"CURLING FACTOR" INHIBITS FUNGAL GROWTH —PERMITS OUTGROWTH OF HEALTHY TISSUE

Hyphal (filamental) tips of fungi are curled, contorted and stunted by FULVICIN.[3] Growth ceases, further penetration of keratin halts, and the fungal disease is arrested.



Fungus immobilized by FULVICIN is cast off as keratin grows out and sloughs off. Healthy tissue replaces infected keratin of skin, hair or nails.

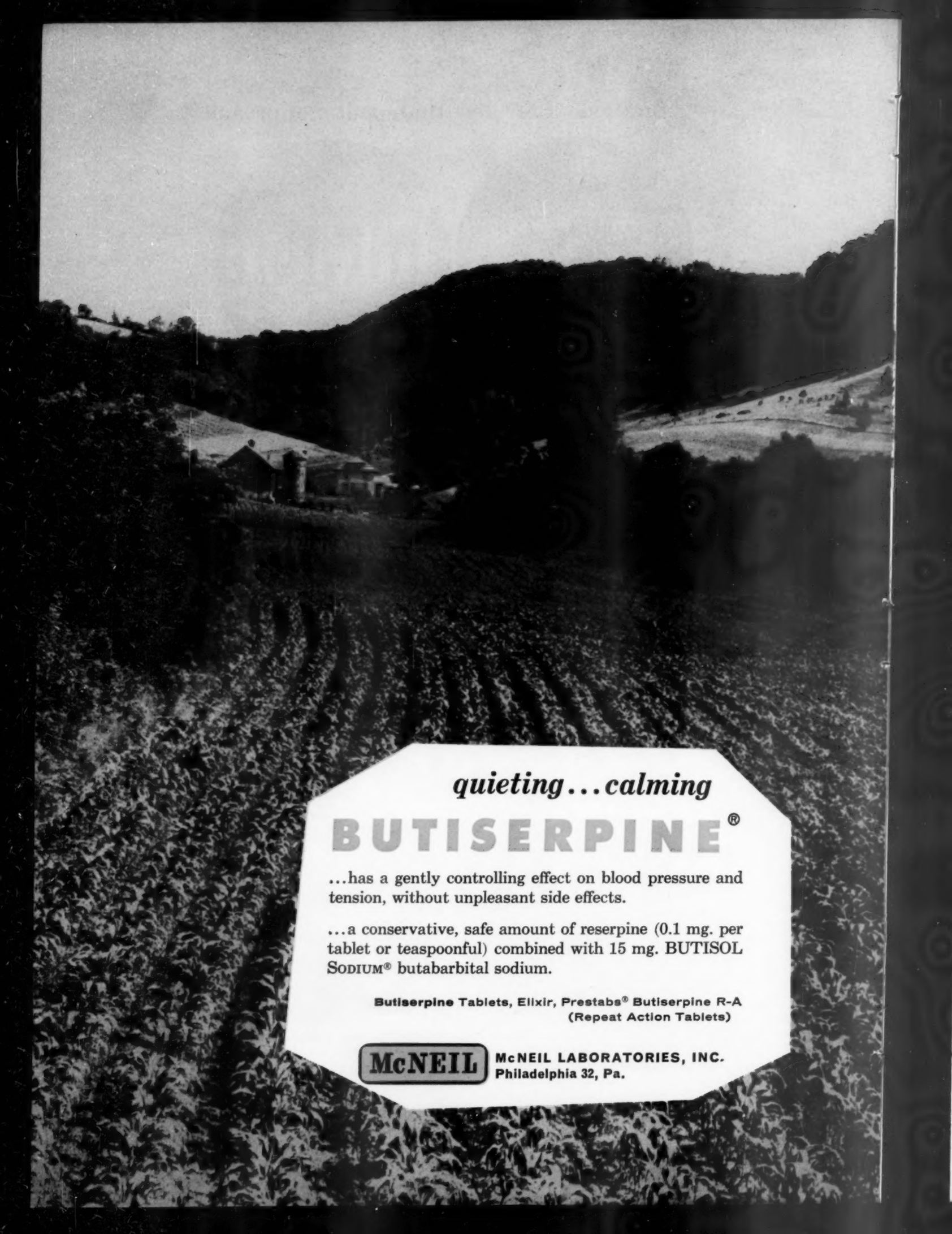
Packaging: FULVICIN Tablets, 250 mg., bottles of 30.

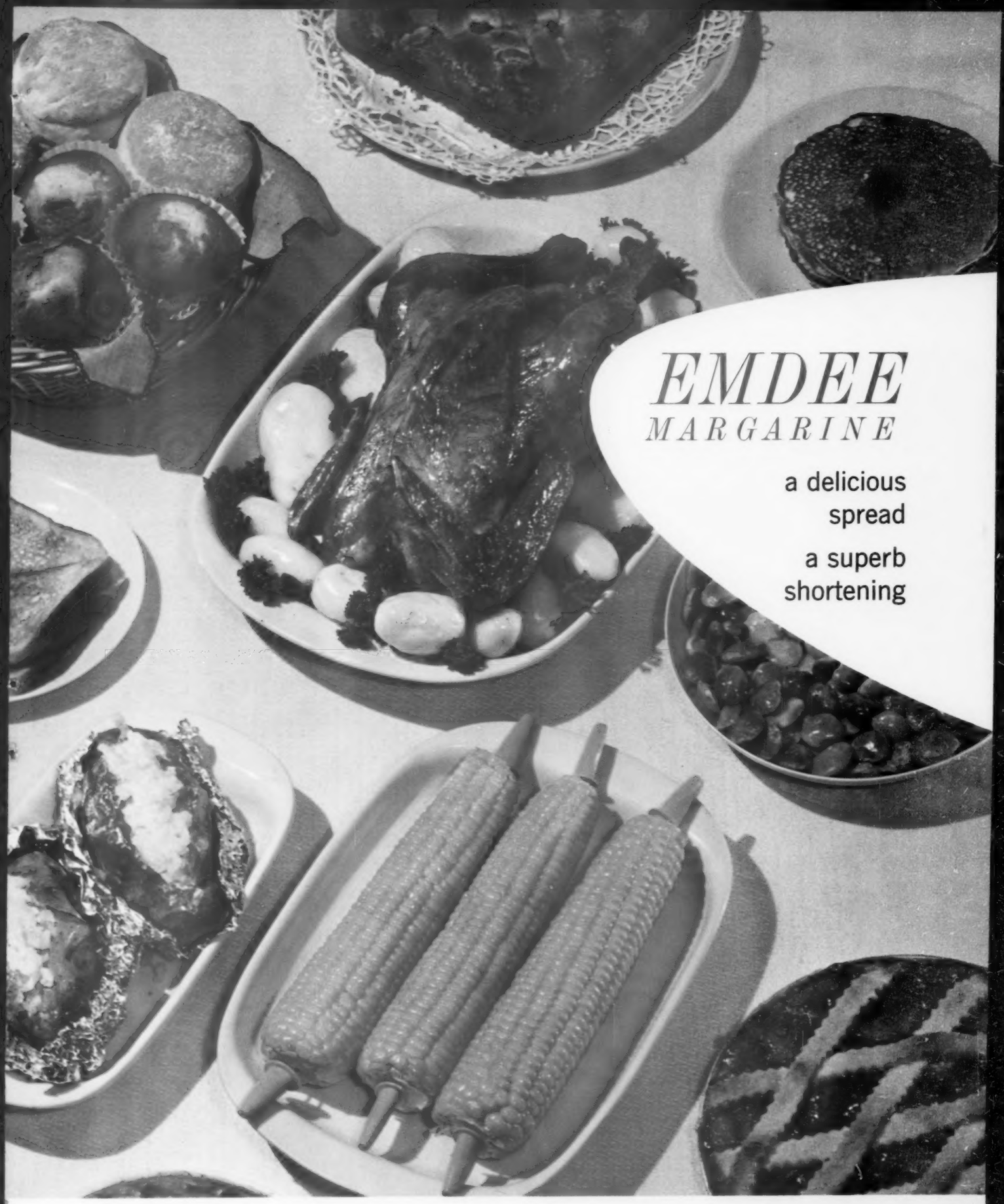
References: (1) Williams, D. I.; Marten, R. H., and Sarkany, I.: Lancet *2*:1212, 1958. (2) Gentles, J. C.; Barnes, M. J., and Fantes, K. H.: Nature *183*:256, 1959. (3) Brian, P. W.; Curtis, P. J., and Hemming, H. G.: Tr. Brit. Mycol. Soc. *29*:173, 1946.

SCHERING CORPORATION • BLOOMFIELD, NEW JERSEY

*T.M.

S-221


quieting...calming
BUTISERPINE®
...has a gently controlling effect on blood pressure and tension, without unpleasant side effects.
...a conservative, safe amount of reserpine (0.1 mg. per tablet or teaspoonful) combined with 15 mg. BUTISOL SODIUM® butabarbital sodium.
Butiserpine Tablets, Elixir, Prestabs® Butiserpine R-A (Repeat Action Tablets)
McNEIL
McNEIL LABORATORIES, INC.
Philadelphia 32, Pa.



and the margarine clinically proved to

lower cholesterol levels

EMDEE™ MARGARINE

substituted for ordinary spreads and shortenings

lowers cholesterol levels

Recent investigations demonstrate how effectively cholesterol levels can be significantly reduced by the simple substitution of Emdee Margarine for spreads and shortenings ordinarily used in the diet.

Eighty per cent of Emdee Margarine's fat content is pure corn oil, whose natural content of polyunsaturated fatty acids has not been destroyed by hydrogenation.* Approximately 45% of its fat content is linoleic acid, an important substance in the control of blood cholesterol levels.

When a patient's intake of saturated fats should be reduced, he and his family will welcome Emdee Margarine. It restores natural flavor to a cholesterol-reducing diet and eliminates the chore of preparing special dishes for one member of the family.

On bread, toast and crackers Emdee Margarine has the same taste as other fine spreads, and a firm, smooth texture. It brings back the familiar flavor to baked potatoes, vegetables and popcorn. It can be used for braising, baking, roasting and sautéing, and in white sauces and frostings. It has won praise from Home Economics experts, who found that Emdee Margarine is a high-quality shortening.

Packaged in one-pound cans to protect its fresh taste and firm texture, Emdee Margarine is *available only in pharmacies.*

References: 1. Terman, L. A.: Dietary management of hypercholesterolemia, Geriatrics *14*:111 (Feb.) 1959. 2. Boyer, P. A.; Lowe, J. T.; Gardier, R. W., and Ralston, J. D.: A new dietary management of hypercholesterolemia, J.A.M.A., in press. 3. Vail, Gladys E.: Cooking with fats high in polyunsaturated fatty acids, J. Am. Dietet. A. *35*:119 (Feb.) 1959.

Reprints of these articles on Emdee Margarine are available on request.

PITMAN-MOORE COMPANY • DIVISION OF ALLIED LABORATORIES, INC.
INDIANAPOLIS 6, INDIANA

*Special process protected by U.S. Patent No. 2,890,959

day and night—ulcer control with **B.I.D.** *dosage*

Just one 10 mg. Daricon tablet in the morning, and one at night before retiring, keeps your patient free from the pain and discomfort caused by gastrointestinal spasm, hypermotility, and hypersecretion.

Daricon is a remarkably potent and well tolerated antisecretory/antimotility agent. Its *naturally* prolonged action provides day and night relief of pain and symptoms associated with peptic ulcer, functional bowel syndrome, biliary tract dysfunctions, and other gastrointestinal disorders characterized by spasm, hypermotility, and hypersecretion.

EVEN REFRACTORY CASES RESPOND

new **DARICON***

oxyphencyclimine hydrochloride

Pfizer Science for the world's well-being™

Pfizer Laboratories
Division, Chas. Pfizer & Co., Inc.
Brooklyn 6, New York

References: 1. Finkelstein, M., et al.: J. Pharmacol. & Exper. Therap. 125:330 (April) 1959. 2. McHardy, G., et al.: Postgrad. Med., in press. 3. Winkelstein, A.: Amer. J. Gastroenterol., in press. 4. Finkelstein, M., et al.: Presented at Fall Meeting, Amer. Soc. Pharmacol. & Exper. Therap., 1958. 5. Leming, B.: Clin. Med. 6:423 (March) 1959.

*Trademark

In hypoprothrombinemia

KONAKION

Rapid action	rate of absorption faster than menadione or derivatives... more potent and lasting effects.
Wide margin of safety	substantially safer than vitamin-K analogues—no kernicterus reported.
Versatility of administration	capsules for oral use...fine aqueous dispersion for parenteral administration.
Compatibility	unlike vitamin-K analogues or similar products, the parenteral form of Konakion is a fine aqueous dispersion compatible with most I.V. vehicles.
Low dosage forms	no excess, no waste—packaged for economical one-time use.

Prophylactically and therapeutically, Konakion is indicated in obstetrics to prevent or control neonatal hemorrhage, to minimize excessive bleeding in surgery, to offset anticoagulant overdosage, and whenever vitamin-K utilization is impaired.

KONAKION®—brand of vitamin K_1
ROCHE® Capsules—5 mg; Ampuls—1 mg/0.5 cc; 10 mg/1 cc; 25 mg/2.5 cc

ROCHE LABORATORIES • Division of Hoffmann-La Roche Inc • Nutley 10, New Jersey

IN STRESS CONDITIONS SUCH AS:

Spontaneous abortion
Inflammatory diseases
Infectious diseases
Cardiovascular diseases
Metabolic diseases

CAPILLARY AND VASCULAR DAMAGE ARE COMMON FINDINGS

In these stress conditions whether caused by nutritional deficiencies, environment, drugs, chemicals, toxins, virus or infections

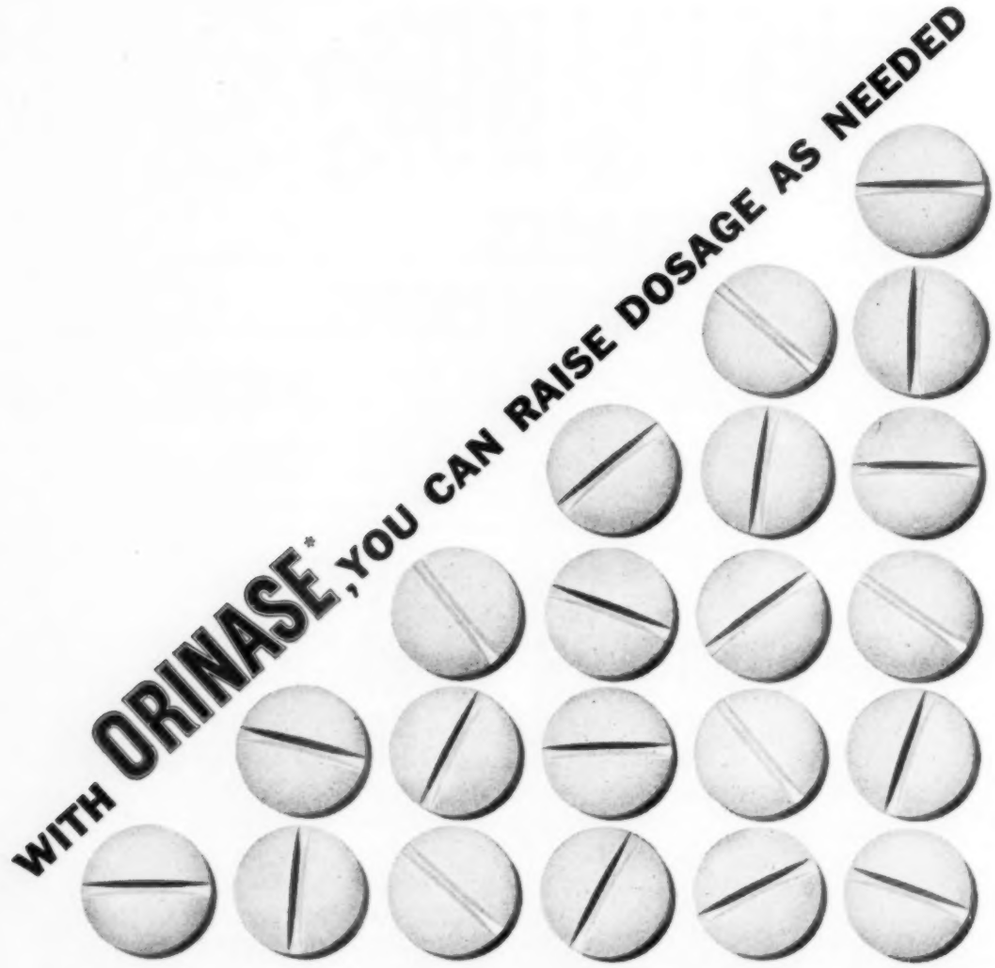
HESPERIDIN, HESPERIDIN METHYL CHALCONE or LEMON BIOFLAVONOID COMPLEX

are indicated as therapeutic adjuncts for the control and management of the associated capillary and vascular damage.

Sunkist and Exchange Brand Hesperidin and Lemon Bioflavonoid Complex are available to the medical profession in specialty formulations developed by leading pharmaceutical manufacturers.

Sunkist Growers

PRODUCTS SALES DEPARTMENT
PHARMACEUTICAL DIVISION
ONTARIO, CALIFORNIA



without running the risk of untoward effects

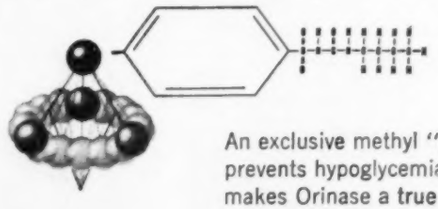
Experience with other oral antidiabetes agents has created some confusion about Orinase dosage. Here are three points worth remembering:

1. The recommended daily dosage range for Orinase extends from 0.5 to 3 Gm. A prominent New York diabetician recently commented, "Most of the referrals I am getting are patients who require only the increasing of their Orinase dosage to 2 or 2.5 Gm. per day—sometimes 3."

2. Although increasing the daily dosage **beyond** 3 Gm. rarely improves control, neither does it increase Orinase's low incidence of unwanted side effects. Selected diabetics given **6 to 10 Gm. daily for sixty to ninety days** showed no signs of toxicity.

3. In patients in whom maintenance dosage has been established, Orinase lowers the blood sugar to normal levels but almost never beyond that point. In other words, Orinase is a true euglycemic agent.

*TRADEMARK, REG. U. S. PAT. OFF.—TOLBUTAMIDE, UPJOHN



An exclusive methyl "governor" prevents hypoglycemia . . . makes Orinase a true euglycemic agent.

Upjohn

The Upjohn Company
Kalamazoo, Michigan

wherever the 4 winds blow

new 4 mg.

POLARAMINE® REPETABS®

For day-to-day relief and maintenance in allergic reactions with these 4 major benefits

High degree of antihistamine efficacy—daylong or nightlong protection with a single 4 mg. REPETAB / Low dosage—lower than with other antihistamines / High therapeutic index (3380)—highest of all antihistamines / Low incidence of side effects—much lower than with other antihistamine preparations

4 mg. POLARAMINE REPETABS in bottles of 100 and 1000

SYMBOL OF THE ONE-DOSE CONVENIENCE YOU WANT FOR YOUR PATIENT.

• PROMPT REPETAB RELIEF • LASTS ALL DAY OR NIGHT

Schering

SCHERING CORPORATION • BLOOMFIELD, N. J. EN1482-9

Nuclear-Chicago's experience in manufacturing medical instruments for detecting and measuring radioactivity began with the first hospitals to employ radioisotopes in diagnostic tests. From that time on, *quality* and *dependability* in design, manufacture, and service have made us the world's leading supplier of instruments for nuclear clinical and diagnostic use in medicine. Our specially trained medical sales and service force covers every state and most countries of the free world.

We invite you to call on our experience at any time for assistance in initiating radioisotope procedures or in modernizing your present facilities to cover new applications of radioisotopes. Our General Catalog R describes in detail over fifty medical instruments, accessories, and complete laboratories to cover every possible need in diagnostic applications of radioisotopes. If you would like to receive a personal copy for your files, just drop us a card or letter—there is no obligation.

Fine Instruments - Research Quality Radiochemicals

nuclear-chicago
CORPORATION

253 WEST ERIE STREET • CHICAGO 10, ILLINOIS

even if your patient is a mud chicken†

†surveyor, to non-engineers

he won't be mired for long once he's on

PARAFON*

PARAFLEX® + TYLENOL®

for muscle relaxation *plus* analgesia

and in arthritis

PARAFON* with Prednisolone

McNEIL

McNeil Laboratories, Inc • Philadelphia 32, Pa.

prescribe PARAFON in low back pain —sprains—strains—rheumatic pains

Each PARAFON tablet contains:
PARAFLEX® Chlorzoxazone‡ . . 125 mg.
Specific for skeletal muscle spasm
TYLENOL® Acetaminophen . . 300 mg.
The analgesic preferred in musculoskeletal pain

Supplied: Tablets, scored, pink, bottles of 50.

Dosage: Two tablets three or four times a day.

Each PARAFON WITH PREDNISOLONE tablet contains: PARAFLEX® Chlorzoxazone‡ 125 mg., TYLENOL® Acetaminophen 300 mg., and prednisolone 1.0 mg.

Supplied: Tablets, scored, buff colored, bottles of 36.

Dosage: One to two tablets three or four times a day.

Precautions: The precautions and contraindications that apply to all steroids should be kept in mind when prescribing PARAFON WITH PREDNISOLONE.

®trade-mark ‡U. S. Patent Pending

251A53

Bright
new
star
in the
antibacterial
firmament

the first nitrofuran effective orally in systemic bacterial infections

ALTAFUR™

brand of furaltadone

Effective clinically in upper respiratory infections, pneumonias, soft tissue infections, bacteremia/septicemia, osteomyelitis, wound infections and pyodermas.

Effective in vitro against the following organisms (isolated from clinical infections listed above):

Organism	*Sensitive*	*Resistant*	*% Sensitive*
Staphylococci*	181	1	*99.4*
Streptococci	65	1	*98.5*
D. pneumoniae	14	0	*100.0*
Coliforms	34	3	*91.8*
Proteus	5	5	*50.0*
A. aerogenes	8	0	*100.0*
Ps. aeruginosa	5	4	*55.5*

*Includes many strains resistant to antibiotics.

As with all nitrofurans in *years* of extensive clinical use, there is little or no development of bacterial resistance with ALTAFUR.

NITROFURANS—a unique class of antimicrobials—
neither antibiotics nor sulfonamides

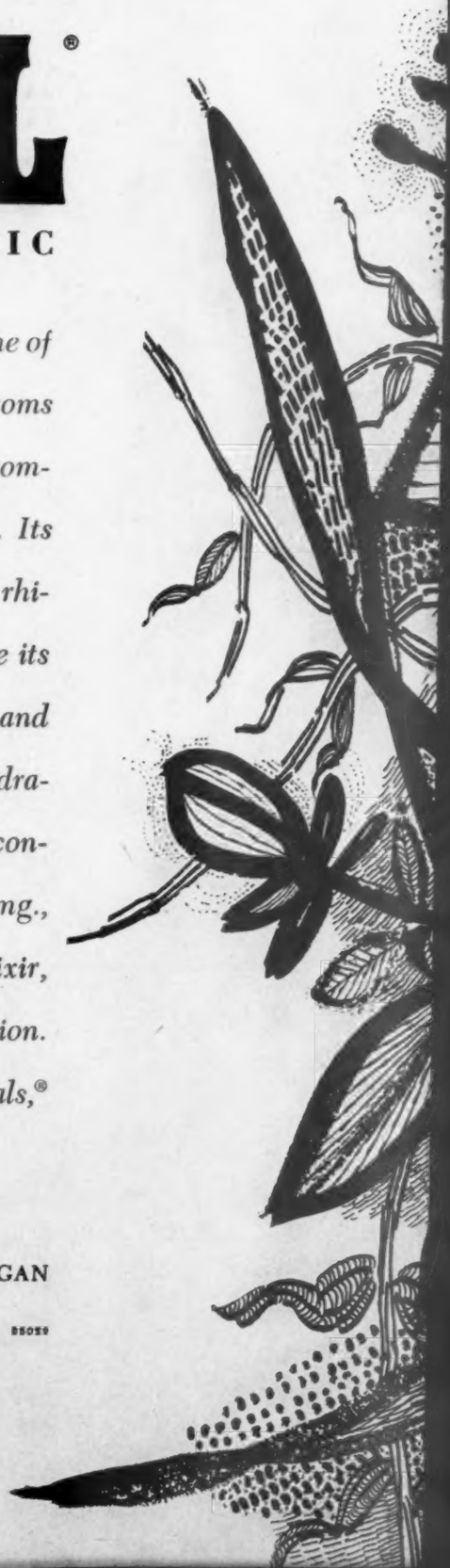
EATON LABORATORIES, NORWICH, NEW YORK

helps them weather the hay fever season

BENADRYL®

ANTIHISTAMINIC-ANTISPASMODIC

gives fast, comprehensive relief of allergic symptoms. At this time of year pollens from trees, grasses, or weeds cause distressing symptoms in allergic patients. You can help your patients to enjoy greater comfort during the hay fever season by prescribing BENADRYL. *Its potent antihistaminic action rapidly relieves nasal blockage, rhinorrhea, sneezing, itching, and related allergic reactions, while its atropine-like antispasmodic action swiftly suppresses bronchial and gastrointestinal spasms.* BENADRYL *Hydrochloride (diphenhydramine hydrochloride, Parke-Davis) is available in a variety of convenient forms including: Kapseals,® 50 mg. each; Kapseals, 50 mg., with ephedrine sulfate, 25 mg.; Capsules, 25 mg. each; Elixir, 10 mg. per 4 cc.; and Emplets,® 50 mg. each, for delayed action. For parenteral therapy,* BENADRYL *Hydrochloride Steri-Vials,® 10 mg. per cc.; and Ampoules, 50 mg. per cc.*

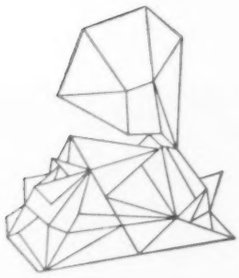


PARKE, DAVIS & COMPANY · DETROIT 32, MICHIGAN

B50X9

PURE ANTIHISTAMINE ACTION NOW A PHARMACOLOGIC FACT BECAUSE DĪSOMER SHEDS THE MOLECULAR DROSS

NEW...IN THE TREATMENT OF ALLERGIC DISORDERS



- *"...high therapeutic index"*[1]
- *unsurpassed clinical efficacy*
- *highly effective in exceptionally small doses*
- *side effects reduced to placebo level*

Disomer....a major scientific advance in the pharmacology of antihistamines!

DISOMER was described as being *"...as close to a pharmacologically pure form of histamine antagonist as the chemist can produce."*[1] Incorporating the newest knowledge of structure-function relationships, DISOMER comes closest thus far to the therapeutic ideal of pure antihistamine activity. DISOMER represents the *d*-isomer of racemic brompheniramine maleate. In shedding the *l*-isomer a high point in clinical effectiveness is achieved while side effects are reduced to the placebo level.

Therapeutic results have been noteworthy with 88% effectiveness reported.[2] Equally noteworthy is the virtual absence of clinically significant adverse reactions. Indeed, the sole side effect reported was occasional, mild drowsiness in only 5% to 6% of patients.

With DISOMER your allergic patient remains your alert patient while enjoying unsurpassed freedom from allergic symptoms. Ready now for your prescription—DISOMER is available in a variety of dosage forms to fit your patients' individual requirements.

Availability:

DISOMER CHRONOTAB*	6 mg.
DISOMER CHRONOTAB*	4 mg.
DISOMER Tablets	2 mg.
DISOMER Syrup	2 mg. per 5 cc.

Usual dosage:

6 mg. CHRONOTAB	b.i.d.
4 mg. CHRONOTAB	t.i.d.
2 mg. Tablet	q.i.d.
Syrup 1 teaspoonful	q.i.d.

**Chronotab* is White's repeat-action tablet.*

References: (1) Gould, A. H. and Long, D. L.: Clinical Pharmacology and Therapeutic Use of Dexbrompheniramine Maleate (Disomer), a new Histamine Antagonist (submitted for publication). (2) Medical Department, White Laboratories, Inc.

WHITE LABORATORIES, INC.
Kenilworth, New Jersey

White's

DISOMER

DEXBROMPHENIRAMINE MALEATE

...sheds the molecular dross

RELIEVES ANXIETY IN HYPERTENSIVE PATIENTS *without producing depression*

Miltown relieves mental pressure which often aggravates symptoms of hypertension and impairs effectiveness of antihypertensive therapy.

Combined with specific therapy, Miltown provided greater over-all improvement in hypertensive patients than antihypertensive therapy alone.[1,2] In 58 patients receiving combined therapy, over 90% (including moderate and severe cases) benefited from relief of headache, nervousness, palpitations, insomnia, weakness and dizziness.[1,2]

Miltown was found "a useful adjunct in the treatment of the psychogenic and neurogenic components of hypertension."[3]

Miltown®

meprobamate (Wallace)

- does not cause depression
- does not interfere with heart rate, blood pressure, respiration, G.I. function or other autonomic mechanisms

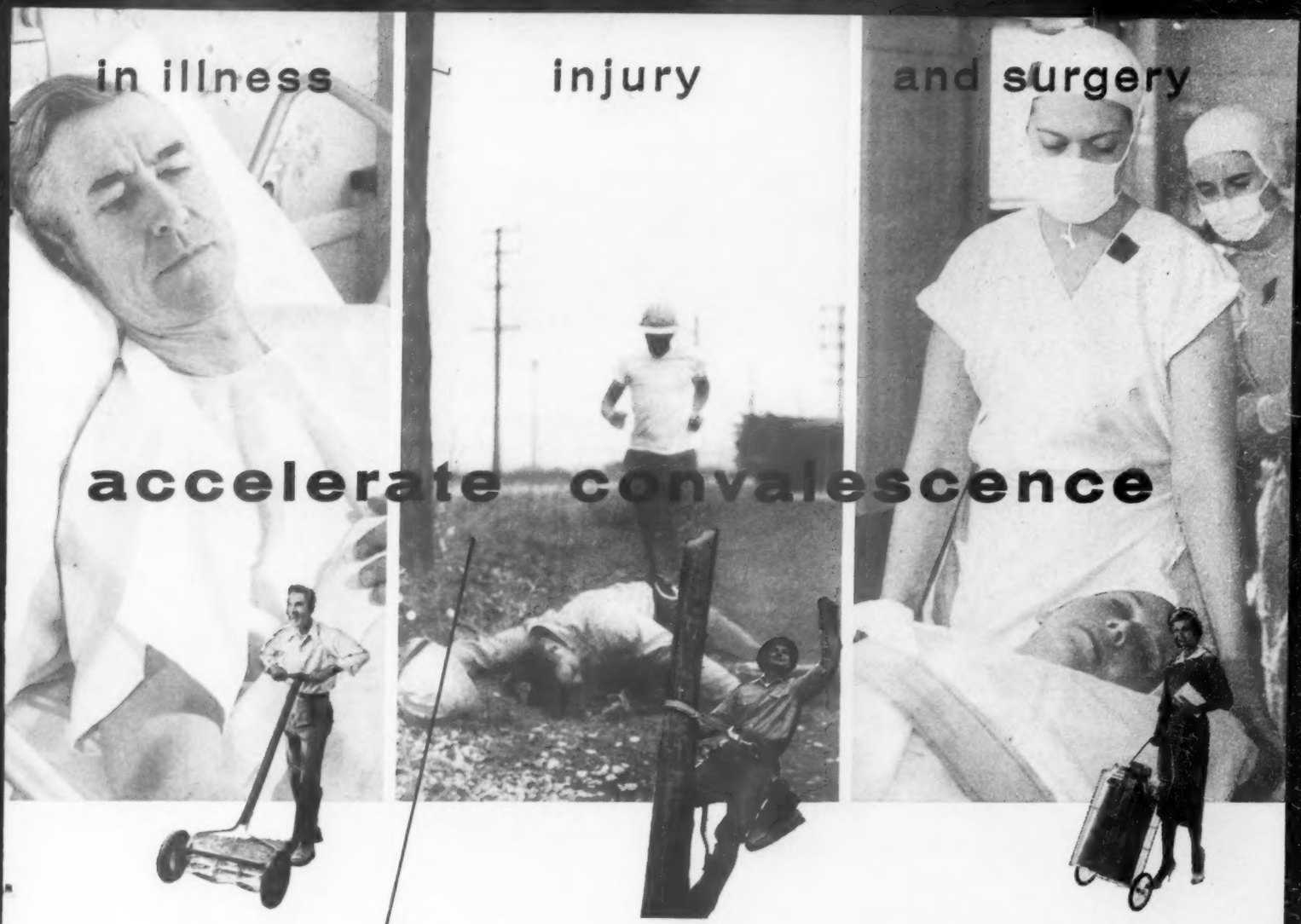
1. Nussbaum, H. E., Leff, W. A., Mattia, V. D., Jr. and Hillman, E.: Am. J. M. Sc. *234*:150, Aug. 1957. 2. Dunsmore, R. A., Dunsmore, L. D., Bickford, A. F. and Goldman, A.: Am. J. M. Sc. *233*:280, March 1957. 3. Boyd, L. J., Huppert, V. F., Mulinos, M. G. and Hammer, H.: Am. J. Cardiol. *3*:229, Feb. 1959.

SUPPLIED: 400 mg. scored and 200 mg. sugar-coated tablets in bottles of 50. Also available as MEPROSPAN* (Miltown *continuous release* capsules). *TRADE-MARK

Literature and samples on request.

CM-9204

WALLACE LABORATORIES • *New Brunswick, N. J.*



"The ability of a patient to recover from an illness, injury, or operation is closely related to his previous and current nutrient supply."[1]

with **Sustagen®**

Complete food, Mead Johnson

powder

. . . you can supply generous amounts of all known essential nutrients in convenient concentrated form. Your patient's recovery time is shortened, and your diet problems are simplified when you use Sustagen . . .

- as a complete liquid diet
- as a basis for soft or bland diets
- to fortify other special diets

orally or by nasogastric tube . . . just add water

1. Halpern, S. L.: Ann. New York Acad. Sc. 63: 147-164 (Oct. 28) 1955.

Mead Johnson

Symbol of service in medicine

SU-559M

AN AMES CLINIQUICK
CLINICAL BRIEFS FOR MODERN PRACTICE

THE CHANGE TO ORAL ANTIDIABETIC THERAPY

...does not reduce the need for attention to *diet, tests for sugar* in the urine, and *tests for acetone* in the urine...*

*Duncan, G. G.: Pennsylvania M. J. *61*:46, 1958.

TEST DAILY
FOR GLYCOSURIA

COLOR-CALIBRATED
CLINITEST®
BRAND Reagent Tablets

the standardized urine-sugar test
for reliable quantitative estimations—better control

- established "plus" system covers entire critical range—includes ¾% (++) and 1% (+++)
- standard blue-to-orange spectrum long familiar to diabetics

available: CLINITEST Reagent Tablets • Bottles of 36 • Boxes of 24 (Sealed in Foil) • CLINITEST Urine-Sugar Analysis Set

TEST DAILY
FOR KETONURIA

ACETEST®
BRAND Reagent Tablets

specific for ketone bodies • no false positives

- one drop of urine...one tablet...a few seconds detects both acetoacetic acid and acetone

available: ACETEST Reagent Tablets—bottles of 100 and 250.
also available as "dip-and-read" test—KETOSTIX® Reagent Strips, bottles of 90.

AMES
COMPANY, INC
Elkhart • Indiana
Toronto • Canada

64059

women of childbearing age... and growing children... may be

OVERDRAWN AT THE BLOOD BANK

Women of menstrual age and growing children have higher iron requirements than other individuals. Hence iron-deficiency anemias occur most often in these groups. Many clinicians recognize that most women need a hematinic for six weeks each year during reproductive years.

Livitamin, with peptonized iron and B complex, offers an excellent formula to restore depleted iron reserves in both adults and children. Peptonized iron is well absorbed and stored, and better tolerated than ferrous sulfate. B complex and other factors provide nutritional support.

LIVITAMIN®

with Peptonized Iron

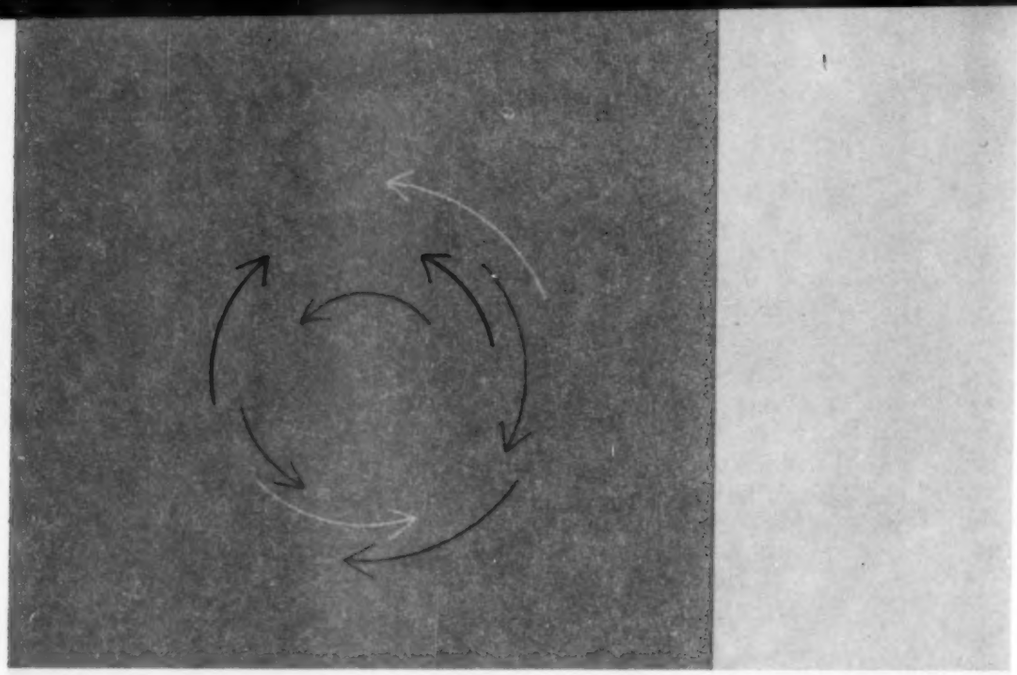
FORMULA: Each fluidounce contains:

Iron peptonized (Equiv. in elemental iron to 71 mg.)	420 mg.
Manganese citrate, soluble	158 mg.
Thiamine hydrochloride	10 mg.
Riboflavin	10 mg.
Vitamin B_{12} Activity (Derived from Cobalamin conc.)	20 mcg.
Nicotinamide	50 mg.
Pyridoxine hydrochloride	1 mg.
Pantothenic acid	5 mg.
Liver fraction 1	2 Gm.
Rice bran extract	1 Gm.
Inositol	30 mg.
Choline	60 mg.

SUPPLIED IN LIQUID OR CAPSULE.

The S.E. MASSENGILL Company

BRISTOL, TENNESSEE • NEW YORK • KANSAS CITY • SAN FRANCISCO



Livitamin assures patient acceptance because it is highly palatable. Peptonized iron provides a virtually predigested form of iron. Recent studies* show peptonized iron has these advantages:

- Rapid response in iron-deficiency anemias
- Non-astringent
- Absorbed as well as ferrous sulfate
- Better gastric toleration than ferrous sulfate
- Less constipating than ferrous sulfate

LIVITAMIN®

with Peptonized Iron

...the preferred hematinic

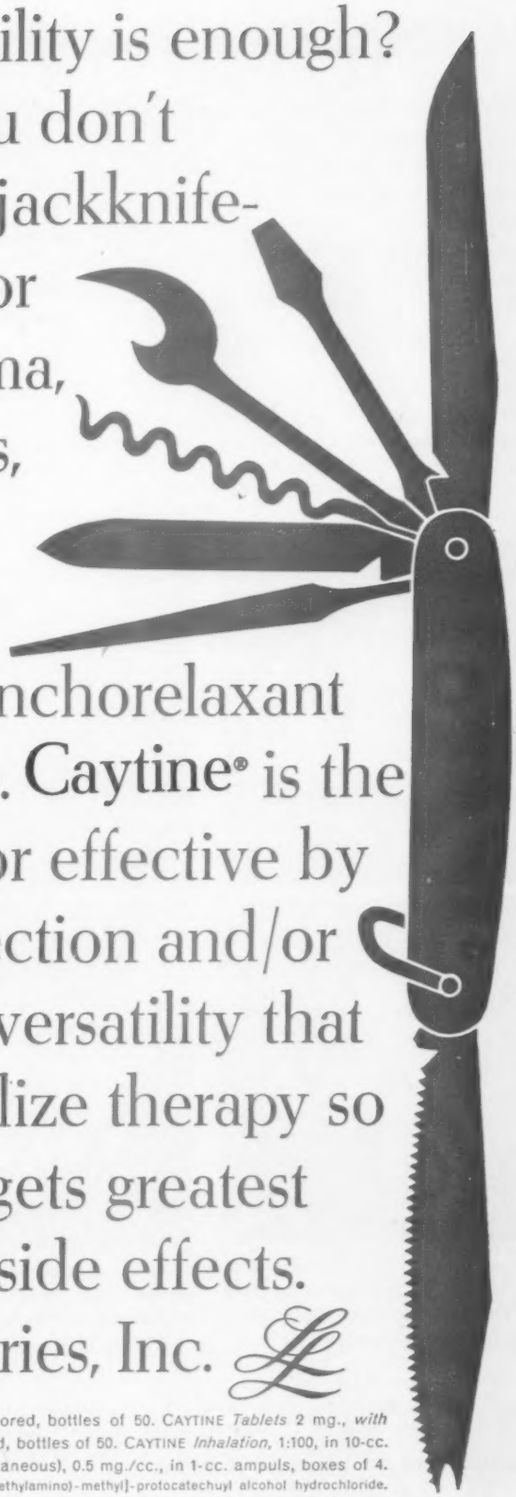
*Keith, J.H.: Utilization and Toxicity of Peptonized Iron and Ferrous Sulfate, Am. J. Clin. Nutrition 1:35 (Jan.-Feb., 1957).

The S. E. MASSENGILL Company BRISTOL, TENNESSEE

NEW YORK • KANSAS CITY • SAN FRANCISO

How much versatility is enough? That depends. You don't ordinarily need a jackknife-of-*all*-trades. But for asthma, emphysema, chronic bronchitis, bronchiectasis, you do need the most versatile bronchorelaxant you can prescribe. Caytine® is the first bronchodilator effective by mouth and/or injection and/or inhalation. Here's versatility that lets you individualize therapy so that each patient gets greatest relief with fewest side effects.

Lakeside Laboratories, Inc.



CAYTINE—*3 effective forms:* CAYTINE *Tablets Plain,* 2 mg., scored, bottles of 50. CAYTINE *Tablets* 2 mg., *with Pentobarbital,* 32 mg. (warning: may be habit forming), scored, bottles of 50. CAYTINE *Inhalation,* 1:100, in 10-cc. bottles with dropper. CAYTINE *Injection* (intramuscular, subcutaneous), 0.5 mg./cc., in 1-cc. ampuls, boxes of 4. CAYTINE is the only brand of the α[(α-methyl-3,4-methylenedioxyphenethylamino)-methyl]-protocatechuyl alcohol hydrochloride.

48559

for full corticosteroid benefits: new Gammacorten

this arthritic needed Gammacorten

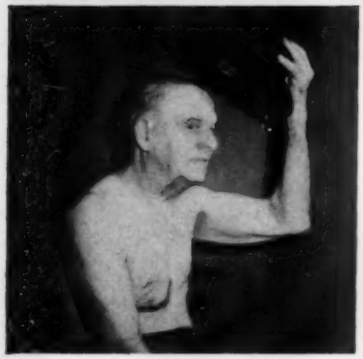
PATIENT M. S., age 81, at time of first visit was in severe pain and very uncomfortable. Complained of swelling of wrists, legs, various joints; there was pain and stiffness in cervical area and lower spine; pain, swelling and limited motion in the fingers; slight ulnar deviation of the hand. He could not raise his arms above the level of his shoulders.

Treatment and Result: After 36 hours of GAMMACORTEN therapy, M. S. had "complete relief." Joint swelling had decreased, pain was almost absent, range of motion had increased dramatically. At the end of the first week of GAMMACORTEN he was free of discomfort and able to return to his job as a porter.

BEFORE GAMMACORTEN: M. S. demonstrates the position necessary to put on his hat (range of motion was so restricted that he could not comb his hair).

BEFORE GAMMACORTEN: His fingers were extremely painful and were so swollen that a size 11 jeweler's ring would not fit over his small finger.

BEFORE GAMMACORTEN: Hands were so painful, stiff and swollen that M. S. could not flatten hand or extend fingers on flat surface.



AFTER ONE WEEK OF GAMMACORTEN: M. S. could put on his hat normally, could comb hair; function near-normal at end of first week of treatment.

AFTER ONE WEEK OF GAMMACORTEN: Size 11 jeweler's ring passes easily over previously swollen joint. At end of first week, "puffiness" had virtually disappeared.

AFTER ONE WEEK OF GAMMACORTEN: Pain completely subsided. M. S. can flatten hand, extend fingers and flex in normal manner without pain.

Photographs used with permission of patient.

How to use Gammacorten

With **GAMMACORTEN**, a full measure of corticosteroid benefit can now be brought to patients who have heretofore obtained less than optimal benefit from adrenocorticoid therapy. In practice, the increased activity of **GAMMACORTEN** means maximal mobility for the arthritic; maximal freedom from attack for the asthmatic; rapid and complete resolution of lesions for the dermatologic patient. Unwanted adrenocorticoid effects are relatively infrequent with **GAMMACORTEN.** Should side effects occur, they can be usually managed by reducing dosage or by supplemental measures.

in arthritis — An initial dosage of 1.5 to 3 mg. per day (2 to 4 tablets divided into 3 or 4 doses). This dosage should be continued until a satisfactory symptomatic response is obtained — usually within 3 or 4 days. After a favorable response has been obtained, reduce dosage by 1/3 every 2 to 3 days until either maintenance dosage is established or therapy can be discontinued. Satisfactory control can often be maintained with as little as 0.75 mg. to 1.5 mg. per day.

in asthma and allergy — **IN STATUS ASTHMATICUS:** Initial daily dosage of **GAMMACORTEN** is 7.5 to 10 mg. (10 to 13 tablets divided into 3 or 4 doses). As soon as the acute state is controlled, reduce dosage slowly by 1/3 to 1/4 until a satisfactory maintenance level is reached or until therapy is discontinued.

IN CHRONIC BRONCHIAL ASTHMA: Initial dosage is 1.5 to 3 mg. of **GAMMACORTEN** per day (2 to 4 tablets divided into 3 or 4 doses). After a satisfactory response has been obtained, decrease dosage by 1/3 every 2 to 3 days until either maintenance level has been determined or therapy can be discontinued. Asthmatics can often be maintained for long periods on as little as 0.75 mg. to 1.5 mg. of **GAMMACORTEN** daily.

IN INTRACTABLE HAY FEVER: Start with 2 to 3 mg. (3 to 4 tablets divided into 3 or 4 doses) of **GAMMACORTEN** per day. Symptoms should be promptly relieved; prolonged maintenance therapy is unnecessary for these self-limiting disorders.

in skin disorders Start with 2 to 3 mg. (3 to 4 tablets divided into 3 or 4 doses) of **GAMMACORTEN** daily. Satisfactory control is usually obtained at this dosage level. In chronic conditions, dosage should be decreased by 1/3 every 2 to 3 days until either a satisfactory maintenance level has been achieved or therapy can be discontinued. In acute or self-limiting disorders, treatment may be discontinued as soon as control has been obtained.

SUPPLIED: **GAMMACORTEN** Tablets, 0.75 mg. S/2704 HK

BEFORE GAMMACORTEN: M. S. could not raise arms above shoulder level; even the degree of motion shown was extremely painful.

AFTER ONE WEEK OF GAMMACORTEN: Range of motion and rotation dramatically increased: M. S. could move arms without pain for the first time in months.

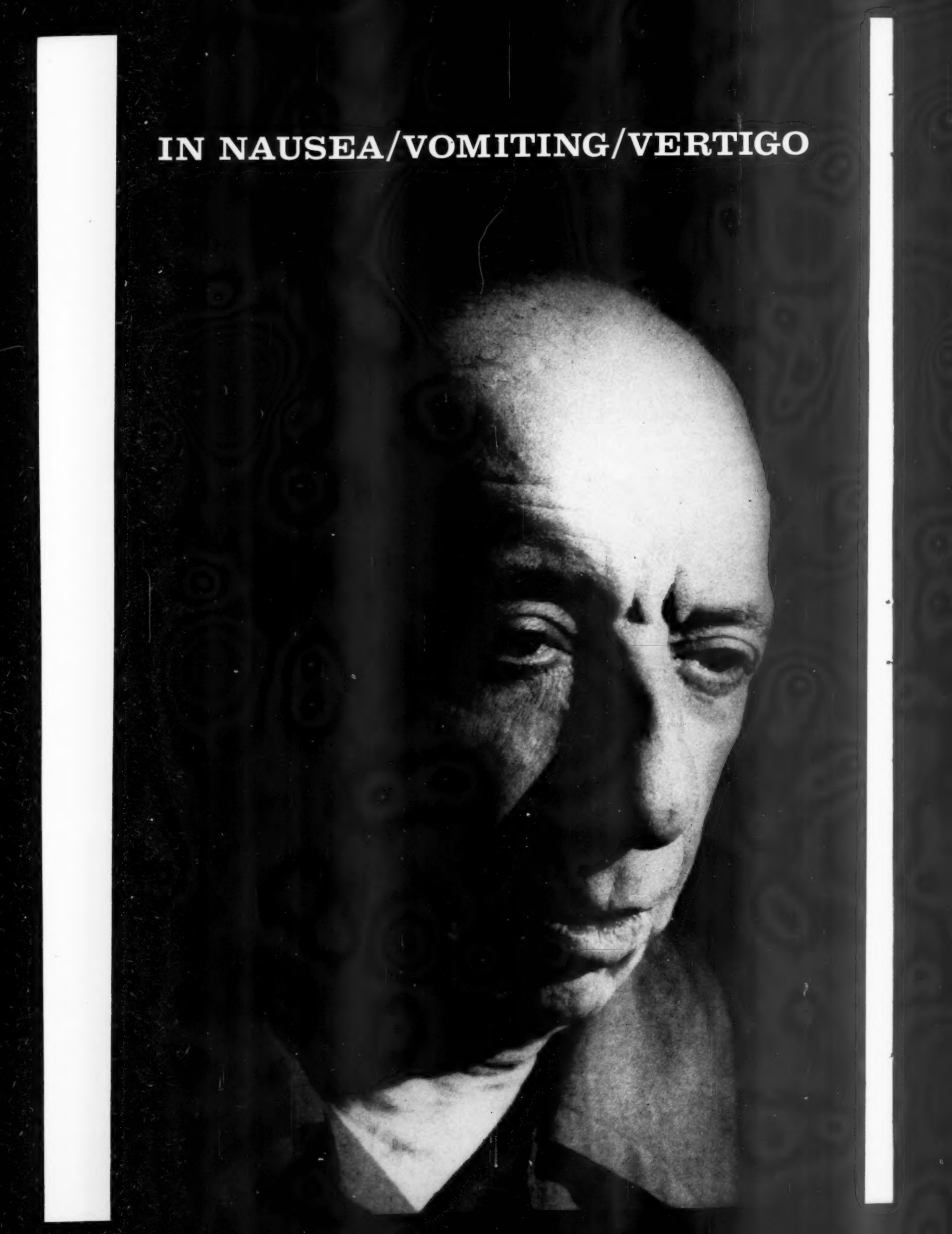
Gammacorten T.M.

(dexamethasone CIBA)

...a potent, highly effective corticosteroid; profound anti-inflammatory activity, with minimal potential for corticosteroid side effects

CIBA
SUMMIT, N. J.

IN NAUSEA/VOMITING/VERTIGO



USE

SPECIFIC
Avoids unnecessarily diffuse or diverse drug action; effective in economical once-a-day dosage

ESTABLISHED
6-year record of successful use in daily practice; consistently favorable reports[1-10]

UNCOMPLICATED
Has no known contraindications; free of hepatic, hypotensive, and hematologic hazards observed with phenothiazines

BONAMINE*

brand of meclizine hydrochloride

SUPPLIED:

BONAMINE Tablets, scored, 25 mg.

BONAMINE Chewing Tablets, mint-flavored, 25 mg.

BONAMINE Elixir, cherry-flavored, ideal for children, 12.5 mg. per teaspoonful (5 cc.).

DOSAGE: Adults, 25 to 50 mg. once a day. Children, usually half the adult dose.

BONAMINE REFERENCES:

1. Moyer, J. H.: M. Clin. North America, Mar., 1957, p. 405.
2. Seidner, H. M.: Illinois M. J. 109:20, 1956.
3. Charles, C. M.: Geriatrics 11:110, 1956.
4. Weil, L. L.: J. Florida Acad. Gen. Practice 4:9, No. 3, 1954.
5. Kinney, J. J.: J. M. Soc. New Jersey 53:128, 1956.
6. Semmons, J. P.: Obst. & Gynec. 9:588, 1957.
7. Conner, P. K., Jr., and Moyer, J. H.: GP 14:124, No. 5, 1956.
8. Deeschner, C. M., et al.: South. M. J. 49:1465, 1956.
9. Mulherin, C. McL., and Bryans, C. I., Jr.: J. M. A. Georgia 45:46, 1956.
10. Report of study by Army, Navy, Air Force Motion Sickness Team: J.A.M.A. 160:755, 1956.

2

PFIZER LABORATORIES Division, Chas. Pfizer & Co., Inc. Brooklyn 6, New York

Pfizer

Science for the world's well-being™

*Trademark

IN UROPATHIES

WHEN PAIN IS PART OF THE PICTURE

Diagram correlates sources of primary urinary pain with areas of referred pain.

Urinary tract pain, at the source or referred, is subject to the rapid analgesic action of the azo dye in Azo Gantrisin. Azo Gantrisin combines dramatic relief of symptoms with proven effective action against infections carried by either blood stream or urine.

Valuable also following urologic manipulation and surgery.

Dosage: Adults—2 tablets four times daily.
Children under 100 lbs—1 tablet four times daily.
Each tablet provides 0.5 Gm Gantrisin plus 50 mg phenylazodiamino-pyridine HCl—bottles of 100 and 500.

AZO GANTRISIN

GANTRISIN®—brand of sulfisoxazole ROCHE®

ROCHE
LABORATORIES
Division of Hoffmann-La Roche Inc.
Nutley 10, N. J.

IT HAPPENS IN THE BEST OF NOURISHED FAMILIES

VITERRA®

meets the specific vitamin-mineral needs of every member of the household — select the form that suits the age and condition of each patient best

VITERRA CAPSULES—comprehensive daily supplement. Bottles of 100.

VITERRA TASTITABS®—can be chewed, dissolved, or swallowed. Bottles of 100.

VITERRA THERAPEUTIC—high potency formula. Bottles of 30 and 100.

VITERRA PEDIATRIC—for infants and small children. 50 cc. Metered-Flow bottle.

Selectively formulated by one of the major producers of bulk vitamins

ROERIG Rx

New York 17, N. Y.
Division, Chas. Pfizer & Co., Inc.
Science for the World's Well-Being

NIAMID*

the mood brightener

Lifts the burden of depression... opens the way for a sunnier outlook

New areas of therapy

NIAMID is clinically effective in a broad range of depressive states, including: involutional melancholia, senile depression, postpartum depression, reactive depression, the depressive stage of manic-depressive disease, and schizophrenic depressive reaction.

A wide variety of psychoneurotic depressions seen in general practice also respond effectively to NIAMID. Depression associated with the menopause and with postoperative states, and depression accompanying chronic or incurable diseases such as gastrointestinal and cardiovascular disorders, arthritis, and inoperable cancer, can now be treated successfully with NIAMID.

NIAMID is also strikingly effective for many complaints, mild or severe, vague or well defined, when due to masked depression rather than to organic disease. This masked depression may take the form of guilt feelings, crying spells or sadness, difficulty in concentration, loss of energy or drive, insomnia, emotional fatigue, feelings of hopelessness or helplessness, loss of interest in normal activity, listlessness, apprehension or agitation, and loss of appetite and weight.

While tranquilizers have had some measure of effectiveness in many of these areas, NIAMID now gives the practicing physician a new, safe drug for the specific treatment of depression without the risk of increasing the depressive symptoms.

New safety

The outstanding safety of NIAMID in extensive clinical trials eliminates the hepatotoxic reactions observed with the first of the monoamine oxidase inhibitors. These reactions have not been seen with NIAMID.

Acute and chronic toxicity studies show this distinctive freedom from toxicity. Moreover, during the extensive clinical trials of NIAMID by a large number of investigators, not only has no liver damage been reported, but only in a very few isolated instances have hypotensive effects been seen.

The absence of toxicity may be the result of the unique carboxamide group in the NIAMID molecule. This structure may explain why NIAMID is excreted largely unchanged in the urine, with only insignificant quantities of potentially free hydrazine being formed. Previously, where a monoamine oxidase inhibitor had been associated with hepatic toxicity, there was some evidence that substantial quantities of free hydrazine were formed in the body.

Background of NIAMID

A major advance in the treatment of mental depression came with a newer understanding of the influence of brain serotonin and norepinephrine on the mood. Levels of both these neuro-hormones are decreased in animals under experimental conditions analogous to depression; relief of these model depressions is seen with a rise in the levels of both serotonin and norepinephrine.

A second advance came with the development of monoamine oxidase inhibitors, substances which raise the cerebral level of both serotonin and norepinephrine. The first of the amine oxidase inhibitors raised the cerebral level of serotonin, but did not appear to raise that of norepinephrine levels proportionately.

Pfizer *Science for the world's well-being™*

PFIZER LABORATORIES

Division, Chas. Pfizer & Co., Inc., Brooklyn 6, N. Y.

Attention at Pfizer Research was then directed to a new drug that would overcome this disadvantage. NIAMID significantly raises the cerebral level of *both* serotonin and norepinephrine under experimental conditions.

The dramatic discovery of NIAMID now makes available an extremely effective, safe antidepressant for the successful treatment of a full range of depressive states.

Precautions

Side effects are most often minor and mild manifestations of central nervous system stimulation, modifiable by reduction in dosage; these may take the form of restlessness, insomnia, headache, weakness, vertigo, dry mouth, and perspiration. Care should be taken when NIAMID is used with chlorothiazide compounds, since hypotensive effects have been noted in some patients receiving combined therapy—even though hypotension has rarely been noted with NIAMID alone. There has been no evidence of liver damage in patients on NIAMID; however, in patients who have any history of liver disease, the possibility of hepatic reactions should be kept in mind.

Dosage and Administration

Start with 75 mg. daily in single or divided doses. After a week or more, revise the daily dosage upward or downward, depending upon the response and tolerance, in steps of one or one-half 25 mg. tablet. Once satisfactory response has been attained, the dosage of NIAMID may be reduced gradually to the maintenance level.

The therapeutic action of NIAMID is gradual, not immediate. Many patients respond within a few days, others satisfactorily in 7 to 14 days. Some patients, particularly chronically depressed or regressed psychotics, may need substantially higher dosages (as much as 200 mg. daily has been used) and prolonged administration before responses are achieved.

Supply

NIAMID is available in: 25 mg., pink, scored tablets in bottles of 100; and 100 mg., orange, scored tablets in bottles of 100.

References

Complete bibliography and Professional Information Booklet are available on request.

*TRADEMARK FOR BRAND OF NIALAMIDE

NIAMID

the mood brightener

Roche announces
the first major breakthrough in the
prophylactic management of pain
in angina pectoris

Ten critical Marplan

Marplan

- *clinically safer*
- *therapeutically more useful*

a new, more active
amine oxidase regulator
which has proven highly valuable
in the symptomatic relief
of angina pectoris

In approximately 70% of cases, Marplan

- reduces the frequency of anginal attacks
- improves exercise tolerance
- lowers nitroglycerin dependence

1. What is Marplan? Marplan is a hydrazine derivative with marked potency in regulating the amine oxidase enzyme system. Already evaluated in over 3500 patients, Marplan has demonstrated marked beneficial effects in the treatment of angina pectoris. Evidence to date indicates that Marplan may also be therapeutically valuable in a number of other important acute and chronic medical conditions. Chemically, Marplan is 1-benzyl-2-(5-methyl-3-isoxazolylcarbonyl) hydrazine.

2. What is the effect of Marplan in angina pectoris? Continued prophylactic administration of Marplan provides symptomatic relief—in the form of pain control and reduced nitroglycerin requirements—in approximately 70 per cent of cases.[1-3] "Excellent effects with relatively small doses" are reported in a group of 31 patients with angina pectoris. In that study, Marplan "afforded greater relief than any other compound in our experience."[3] To date, Marplan prophylaxis has been evaluated in a total of 238 anginal cases. The response rate was 72.7 per cent, with improvement ranging from a reduction in the number of attacks to virtual abolition of the anginal state.[1]

3. What is the effect of Marplan on blood pressure? Marplan should not be used as a hypotensive agent. The possibility of postural hypotension, though relatively infrequent, must be borne in mind.

4. What type of angina case is particularly responsive to Marplan prophylaxis? Marplan has been evaluated in angina of varying severity. It is felt, however, that optimum benefit will be derived in moderately severe to intractable cases.

5. Is the antianginal effect of Marplan the same as its antidepressant action? Marplan is unique in that it exhibits two distinct primary effects: its antianginal action, while biochemically related, is clinically separate from its antidepressive effects.

6. How can one compound have two such seemingly dissimilar effects? The mechanism of action of Marplan and of the other amine oxidase regulators is not yet fully defined. Marplan's pharmacologic effects are secured indirectly: By regulating amine oxidase levels; it inhibits the breakdown of serotonin, norepinephrine and other biologically active amines. In animal experiments, serotonin infusion of the heart muscle produces an increase in the ratio of coronary blood flow to coronary vascular resistance.[4]

questions define the scope of prophylaxis in angina pectoris

7. How should Marplan be given? The usual starting dose is 30 mg daily to be given in single or divided doses. The patient should be observed carefully and individual dosage adjustment made according to response. Many patients will respond quickly to the initial dose of 30 mg daily, and the dosage should then be reduced to 10 or 20 mg daily (or less) for maintenance therapy. In some patients beneficial effects may not be observed for three or four weeks. Since daily doses larger than 30 mg may cause an increase in side effects, such as hypotension and constipation, it is not recommended that higher dosages be employed.

8. What are the precautions? All patients treated with hydrazine derivatives should be kept under close medical supervision. While there is no definite knowledge of a hazard with Marplan, use of this class of agent should be discontinued at the first sign of jaundice or impaired liver function. Periodic liver function tests are advised during hydrazine therapy. These drugs are contraindicated in patients with a history of previous liver disease or impaired liver function. In patients with impaired kidney function, Marplan should be used cautiously to prevent accumulation and should not be used in epileptic patients. Patients receiving a hydrazine in conjunction with drugs such as alcohol, ether, barbiturates, meperidine, cocaine, procaine, and phenylephrine should be more closely supervised.

9. What are the side effects, if any? In one of the largest bodies of clinical material for this new class of drugs, Marplan shows one of the lowest recorded incidences of side effects. Particular attention was focused on attempts to define as precisely as possible amine oxidase inhibitor side effects on a wide range of organs, including liver and bone marrow. Extensive clinical studies have revealed no jaundice or liver damage attributable to Marplan. Nevertheless, since Marplan is an amine oxidase inhibitor, the same precautions should be observed with Marplan therapy as with other amine oxidase inhibitors. Since Marplan is a potent therapeutic agent affecting many enzyme systems of the body, side effects may be expected to occur in a certain percentage of cases. Side effects have rarely been severe enough to necessitate discontinuance of Marplan therapy. However, as with all agents of this type, the patient should be observed for signs of orthostatic hypotension, complaints of dizziness and vertigo, constipation, overactivity, jitteriness, insomnia, peripheral edema, weakness, fatigue, dryness of the mouth, blurred vision and skin rashes.

10. How can patients be transferred from their present anginal prophylaxis? Initially the established nitrite regimen should be maintained, while simultaneously placing the patient on a daily dose of 30 mg Marplan. The patient is to be observed carefully and nitrite intake decreased as pain episodes diminish. Response to Marplan prophylaxis may be delayed for several weeks.

Marplan

Supplied: 10-mg tablets in bottles of 100 and 1,000.

References: 1. Clinical reports on file, Roche Laboratories. 2. W. Hollander and R. W. Wilkins in J. H. Moyer, Ed., *Hypertension*, Philadelphia, W. B. Saunders Co., 1959, p. 399. 3. R. W. Oblath, paper read at American Therapeutic Society, 60th Annual Meeting, Atlantic City, N. J., June 6, 1959. 4. C. W. Crumpton, et al., Conference on Amine Oxidase Inhibitors, New York City, November 20-22, 1958.

MARPLAN™—brand of isocarboxazid ROCHE®

ROCHE LABORATORIES

Division of Hoffmann-LaRoche Inc • Nutley 10 • N.J.

New Practical Guide for the Management of Sports Injuries!

An Unusual Contribution to Your Professional Knowledge

SYMPOSIUM ON

Sports Injuries

Guest Editor: THOMAS B. QUIGLEY, M.D.
Assistant Clinical Professor of Surgery, Harvard Medical School, Boston

Frequency and Nature of Sports Injuries . . . Organized Medicine and Athletics . . . Physical Fitness for Sports . . . The Place of the Trainer in Modern Athletics . . . Athletics and Nutrition . . . Evaluation and Treatment of Muscle Function in Athletic Injury . . . Protective Football Equipment . . . Engineering Research on Protective Headgear . . . Experimental Investigation of Ligament Healing . . . Initial Management of Athletic Injuries to the Head and Neck . . . Eye Injuries . . . Face and Teeth Injuries . . . Arm and Hand Injuries . . . The Mechanics of Some Common Shoulder Injuries in Sports . . . Athletic Injuries to the Shoulder Region . . . The Treatment of Dislocation of the Acromioclavicular Joint . . . Athletic Injuries to the Abdomen and Thorax . . . Athletic Injuries to the Pelvis, Hip and Thigh . . . Sports Injuries to the Genitourinary Tract . . . Injuries to the Knee . . . Ankle Fractures and Ligament Injuries . . . Elbow and Shoulder Lesions of Baseball Players . . . Ski Injuries . . . Can Skin Diving Be Made Safe? . . . Boxing Injuries . . . Athletic Injuries to the Elbow, Forearm, Wrist and Hand.

The Symposium on Sports Injuries is yours—FREE—if you subscribe now to The American Journal of Surgery, the Journal that reports promptly on new operative techniques, new surgical equipment and supplies.

FILL OUT AND MAIL

The American Journal of Surgery
11 East 36th Street,
New York 16, N. Y.

Send me a Free copy of the Symposium on Sports Injuries and enter my subscription to The American Journal of Surgery for one year (12 issues) at $15.00 (Canada $16.00; Foreign $18.00). Send bill.

Name _____

Address _____ City _____ Zone ____ State _____

My specialty is _____

in Turkey,
it's called the 'Turkey trot'

diarrhea by any name

GASTROENTERITIS
BACILLARY DYSENTERY
PARADYSENTERY
SALMONELLOSIS
DIARRHEA OF THE NEWBORN
NONSPECIFIC DIARRHEA
"SUMMER COMPLAINT"

usually responds rapidly to

Cremomycin®

NEOMYCIN-SULFASUXIDINE®-KAOLIN-PECTIN SUSPENSION

for *rapid* relief of virtually all diarrheas

fruit-flavored, readily accepted by patients of all ages*

Neomycin—rapidly bactericidal against most intestinal pathogens, but is relatively ineffective against such diarrhea-causing organisms as Shigella.

SULFASUXIDINE®—an ideal adjunct to neomycin because it is highly effective against Shigella and certain other neomycin-resistant organisms.

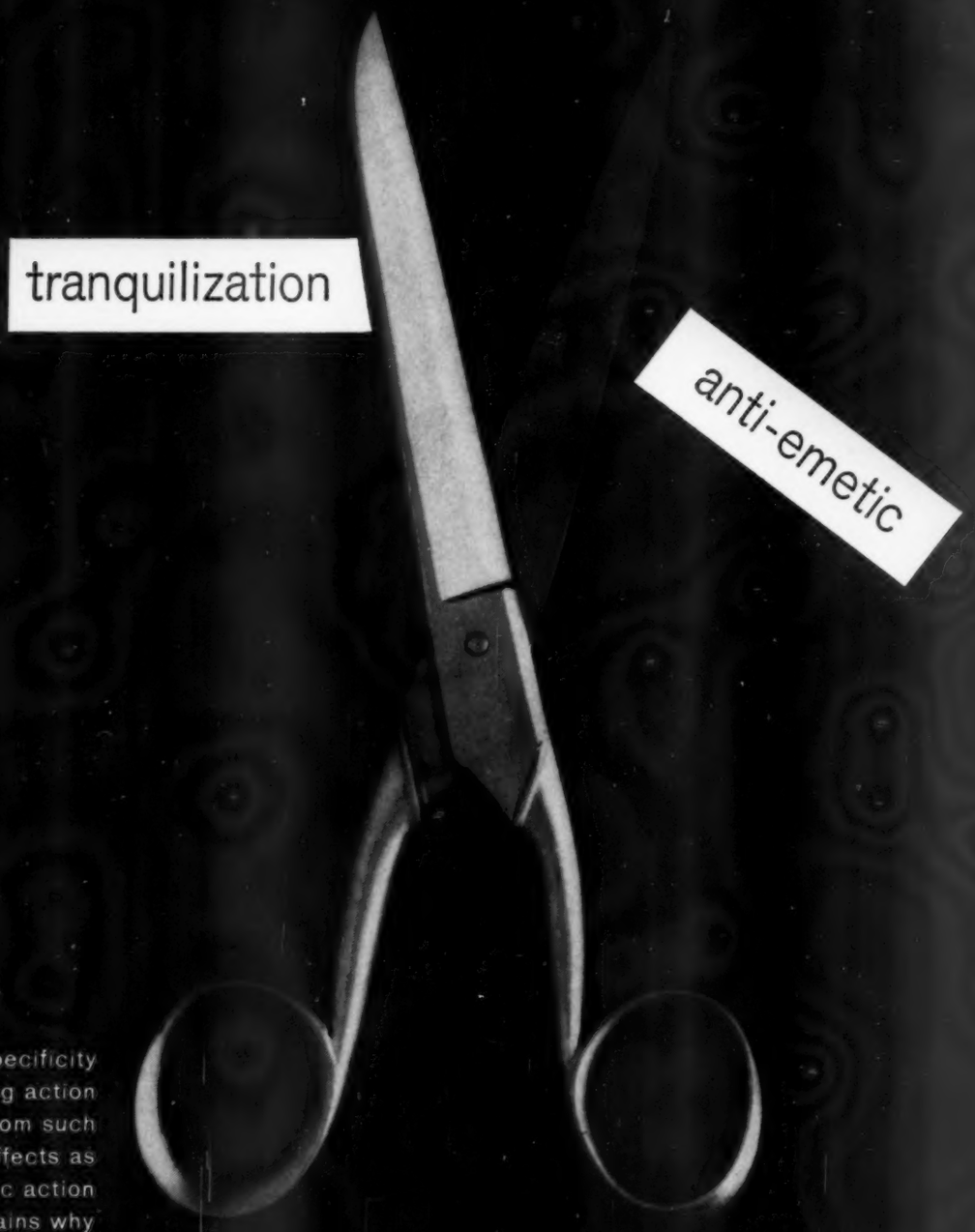
Kaolin and Pectin—coat and soothe the inflamed mucosa, adsorb toxins, help reduce intestinal hypermotility, help provide rapid symptomatic relief.

***For infants, CREMOMYCIN may be administered in the regular bottle feeding since its fine particles easily pass through a standard nursing nipple.**

MSD **MERCK SHARP & DOHME, DIVISION OF MERCK & CO., INC., PHILA. 1, PA.**

CREMOMYCIN AND SULFASUXIDINE (SUCCINYLSULFATHIAZOLE) ARE TRADEMARKS OF MERCK & CO., INC.

NOW . . . SAFER, EFFECTIVE TRANQUILIZER THERAPY



greater specificity
of tranquilizing action
—divorced from such
"diffuse" effects as
anti-emetic action
—explains why

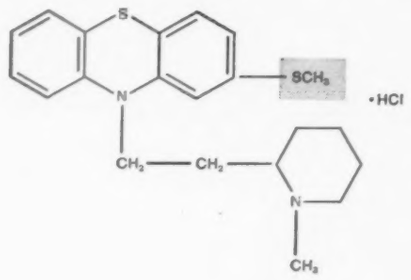
Mellaril

THIORIDAZINE HCl

is virtually free of such toxic effects as jaundice . Parkinsonism . blood dyscrasia

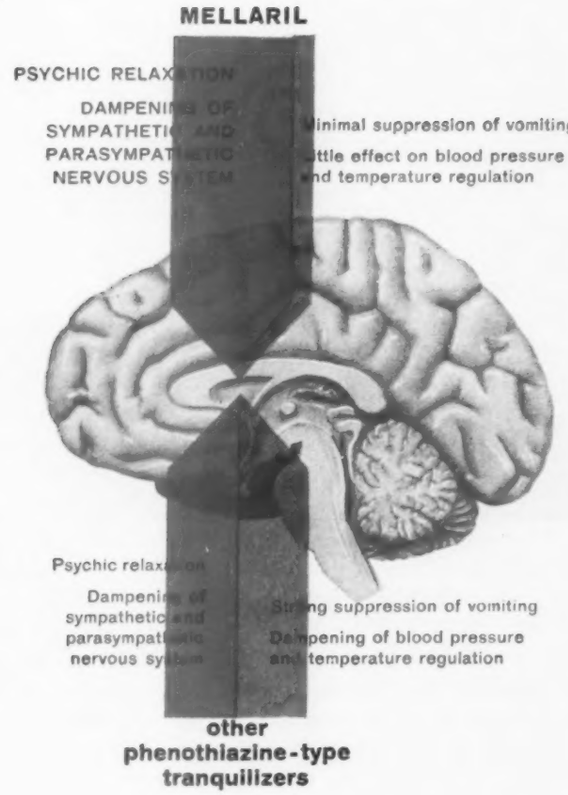
"Thioridazine [MELLARIL] is as effective as the best available phenothiazine, but with appreciably less toxic effects than those demonstrated with other phenothiazines. . . . This drug appears to represent a major addition to the safe and effective treatment of a wide range of psychological disturbances seen daily in the clinics or by the general practitioner."*

a new advance in tranquilization:
greater specificity of tranquilizing action results in fewer side effects



The presence of a thiomethyl radical ($S\text{-}CH_3$) is unique in Mellaril and could be responsible for the relative absence of side effects and greater specificity of psychotherapeutic action. This is shown clinically by:

1 **A specificity of action on certain brain sites in contrast to the more generalized or "diffuse" action of other phenothiazines. This is evidenced by a lack of appreciable anti-emetic effect.**


MELLARIL
PSYCHIC RELAXATION
DAMPENING OF SYMPATHETIC AND PARASYMPATHETIC NERVOUS SYSTEM
Minimal suppression of vomiting
Little effect on blood pressure and temperature regulation
Psychic relaxation
Dampening of sympathetic and parasympathetic nervous system
Strong suppression of vomiting
Dampening of blood pressure and temperature regulation
other phenothiazine-type tranquilizers

2 **Less "spill-over" action to other brain areas — hence, absence of undue sedation, drowsiness or autonomic nervous system disturbances.**

3 **A notable absence of extrapyramidal stimulation.**

4 **Lack of impairment of patient's normal drive and energy.**

5 **Virtual freedom from such toxic effects as jaundice, photosensitivity, skin eruptions, blood forming disorders.**

INDICATION	USUAL STARTING DOSE	TOTAL DAILY DOSAGE RANGE
ADULTS: Mental and Emotional Disturbances:		
MILD—where anxiety, apprehension and tension are present	10 mg. t.i.d.	20-60 mg.
MODERATE—where agitation exists in psychoneuroses, alcoholism, intractable pain, senility, etc.	25 mg. t.i.d.	50-200 mg.
SEVERE—in agitated psychotic states as schizophrenia, manic depressive, toxic psychoses, etc.:		
Ambulatory	100 mg. t.i.d.	200-400 mg.
Hospitalized	100 mg. t.i.d.	200-800 mg.
CHILDREN: BEHAVIOR PROBLEMS IN CHILDREN	10 mg. t.i.d.	20-40 mg.

MELLARIL Tablets, 10 mg., 25 mg., 100 mg.

*Ostfeld, A. M.: Scientific Exhibit, American Academy of General Practice, San Francisco, April 6-9, 1959.

SANDOZ

both blood picture and patient respond to TRINSICON®

Investigators[1,2] have determined that low serum iron may be accompanied by insidious vitamin B_{12} deficiencies which result from subnutrition, increased demand, or lack of intrinsic factor. Coexisting vitamin C deficiencies also have been found.[3]

These studies suggest that an anemia may be multiple in nature—that optimum results would be derived from a combination of therapeutic agents.

Trinsicon offers therapeutic quantities of all known hematinic factors. Prescribe two Pulvules® daily to provide assured response in all treatable anemias.

Trinsicon® (hematinic concentrate with intrinsic factor, Lilly)

1. A. M. A. Arch. Int. Med., *99*:346, 1957.
2. Am. J. Obst. & Gynec., *70*:1309, 1955.
3. Lancet, *1*:448, 1957.

ELI LILLY AND COMPANY • INDIANAPOLIS 6, INDIANA, U.S.A.

919033

The American Journal of Medicine

VOL. XXVII AUGUST, 1959 No. 2

Editorial

Cirrhosis in Alcoholics

THE frequent occurrence of cirrhosis in persons who consume alcoholic beverages to excess is so well known that a relation between alcoholism and cirrhosis has long been suspected. The nature of this relation has not been established, nor is there complete agreement concerning the clinical and pathologic features of the cirrhosis seen in alcoholics. One type, apparently frequent in England and South America, and commonly observed in the voluntary hospitals of this country, usually presents itself first with portal hypertension and ascites. Jaundice and hepatic failure are not necessarily present. The social history may not be unusual and the signs of nutritional deficiencies are not conspicuous. Liver biopsy specimen reveals more or less advanced cirrhosis, often with little if any fatty change, and at autopsy either a diffuse cirrhosis of the Laennec, portal or septal type is noted, or a postnecrotic cirrhosis [*1*] may be found.

Quite different is the course of the alcoholics who have been drinking heavily and eating poorly for weeks or months up to the day they present themselves for treatment. Evidences of nutritional deficiency are most prominent in this group, e.g., beriberi, Wernicke's encephalopathy, "rum fits" and severe macrocytic (folic acid deficiency) anemia. They typically come from "skid row" and are seen in the large charity hospitals of this country; they seem also to be well known among the alcoholics of France, Germany and Italy. Fatty change of the liver is nearly always present and usually of marked degree.

The clinical and pathologic evolution of this latter liver disease in the alcoholic is gradually becoming clearer as the result of animal experiments and serial clinical studies with biopsy. Excessive intake of alcohol is fully accepted as one of the causes of prolonged hepatic steatosis. Excess fat accumulates in the liver as the result either of anoxia, intoxications, or endocrinologic or nutritional disturbances. In the first two conditions the fatty metamorphosis is transient as a rule, and associated with other clinical and pathologic features which are of greater significance for the fate of the patient. Hepatic steatosis produced by the latter two conditions has been frequently considered a precursor of cirrhosis; malnutrition, particularly if caused by an excess intake of calories not balanced by protein and probably by choline, seems of major importance [*2,3*]. The fatty metamorphosis usually disappears rather rapidly during abstinence and normal food intake, especially if it is the only observable abnormality. This histologic disappearance of fat usually is paralleled by an equally rapid clinical improvement [*4*].

[1] MACDONALD, R. A. and MALLORY, G. K. The natural history of postnecrotic cirrhosis. A study of 221 autopsy cases. *Am. J. Med.*, 24: 334, 1958.

[2] BEST, C. H., HARTROFT, W. S. and SELLERS, E. A The protection of the liver by dietary factors. *Gastroenterology*, 20: 375, 1952.

[3] KLATSKIN, G., KREHL, W. A. and CONN, H. O. The effect of alcohol on the choline requirement. *J. Exper. Med.*, 100: 605, 615, 1954.

[4] PHILLIPS, G. B., GABUZDA, G. J., JR. and DAVIDSON, C. S. Comparative effects of a purified and an adequate diet on the course of fatty cirrhosis in the alcoholic. *J. Clin. Invest.*, 31: 351, 1952.

While it appears that the large liver of the alcoholic is frequently caused by excess storage of fat, the original claim [*5*] that fatty metamorphosis as such produces cirrhosis in man has been challenged by many in this country [*6*] and has been contradicted by British investigators [*7–9*]. In experimental animals, especially rats, the transition of fatty metamorphosis of the liver, produced by a high fat, low protein or choline-free diet for instance, to cirrhosis without other known factors is fully established and the pathways have been well traced [*10*]. However, severe fatty metamorphosis has not been shown to progress directly to cirrhosis in man unless other pathologic changes are present as well. Moreover, the vascular supply of the human liver is different from that of the rat liver [*11*]. Therefore, many American investigators believe that an additional link may be required in the transition between hepatic steatosis and cirrhosis.

Some alcoholics, usually the most severe ones, present themselves with clinical evidence of advanced hepatocellular disease, including altered serum protein reactions, low prothrombin concentration, decreased serum concentration of cholesterol esters, and impaired hippuric acid synthesis. Jaundice is usually but not necessarily a prominent feature, and in most instances the degree of bilirubinemia correlates well with the degree of hepatic disease. Anatomically, these acute aggravations with or without severe jaundice are reflected in hepatocellular necrosis usually associated with new formation of reticulum fibers. The necrosis may have the non-specific features of disturbed circulation or bile stasis. More often it exhibits the characteristic histologic picture of a cytoplasmic coagulation. Fine granules are arranged as ramified bodies around the nucleus, the "alcoholic hyaline" of Mallory [*12*]. This is associated with disintegration of cells and accumulation of segmented leukocytes. This specific type of hepatic necrosis is seen rarely, if at all, in non-alcoholics. Both types of necrosis are associated with or followed by diffuse formation of collagenous membranes throughout the lobules. In the course of time, the lobular parenchyma becomes dissected by connective tissue septums, with simultaneous formation of regenerative nodules as the result of the fatty metamorphosis and of the specific and non-specific necrosis. Finally there is transformation into fatty cirrhosis, with uniform involvement of the entire organ. Subsequently, when the fat disappears, the small shrunken liver of Laennec's cirrhosis has developed.

The three phenomena—fatty steatosis, necrosis and fibrosis—thus occur together but may act independently to some extent. Thus, if the fat decreases rather rapidly on proper management, specific and also non-specific necrosis and fibrosis continue in evidence for a considerably longer time and often then become the predominant lesion while clinical evidence of reduced liver function persists. Clinical improvement is slower than with uncomplicated fatty steatosis, which may be associated with fever and some leukocytosis, but a conspicuous increase in white cells to 15,000 or 25,000 per cu. mm. or more is usually associated with histologic necrosis and polymorphonuclear infiltration of the liver substance. Fibrosis alone is best correlated with the evidence of ascites and portal hypertension (superficial abdominal collateral circulation, esophageal varices, splenomegaly and leukopenia). Whether or not fibrosis is reversible is not known. However, patients in whom the liver biopsy specimen shows only fibrosis and nodular regeneration frequently have progressive clinical improvement, although usually it is very gradual.

The varying contributions of fatty metamorphosis, necrosis and fibrosis as well as the different speed of their development account for the great clinical variations in the fatty liver-cirrhosis syndrome. To this must be added intrahepatic cholestasis as an expression of an hepatic injury of as yet uncertain pathogenesis. In some instances, deep jaundice with little other evidence of hepatocellular dysfunction may dominate the picture to create confusion with

[5] Connor, C. L. The etiology and pathogenesis of alcoholic cirrhosis of the liver. *J. A. M. A.*, 112: 387, 1939.

[6] Gyorgy, P. Experimental hepatic injury. *Am. J. Digest Dis.*, 19: 392, 1952.

[7] Davies, J. N. P. Nutrition and nutritional diseases. *Ann. Rev. Med.*, 3: 99, 1952.

[8] Dibble, J. H. Degeneration, necrosis and fibrosis in the liver. *Brit. M. J.*, 1: 833, 1951.

[9] Sherlock, S. Diseases of the Liver and Biliary System, 2nd ed. Oxford, 1958. Blackwell Scientific Publications.

[10] Hartroft, W. S. The sequence of pathologic events in the development of experimental fatty liver and cirrhosis. *Ann. New York. Acad. Sc.*, 57: 633, 1954.

[11] Elias, H. and Popper, H. Venous distribution in livers. *Arch. Path.*, 59: 33, 1955.

[12] Mallory, F. B. Cirrhosis of the liver. *New England J. Med.*, 206: 1231, 1932.

extrahepatic biliary obstruction and to invite unnecessary surgical intervention [*13*].

The acute stage in the fatty liver-cirrhosis syndrome, often clinically mistaken for viral hepatitis, is responsible not only for the transition of fatty liver into cirrhosis but also for the acute deterioration with death, as well as rapid progression in any stage of the syndrome. Younger persons in particular, almost as often female as male, with huge fatty liver may die in a week or two in hepatic failure with deep jaundice, and at autopsy the evidence of necrosis may be insignificant [*14*]. Another example is the patient in whom jaundice of several months' duration is associated with diffuse fiber formation but with as yet incomplete cirrhotic transformation (florid cirrhosis) [*15*].

The mechanism of hepatic necrosis, specific and non-specific, in the fatty liver-cirrhosis syndrome still requires better understanding before a therapy based on etiology can be developed to arrest the necrosis and the transition into the phase of crippling cirrhosis. Even more challenging is the problem of the development of cirrhosis in alcoholics who never have a fatty liver.

CHARLES S. DAVIDSON, M.D.
Thorndike Memorial Laboratory
Boston City Hospital
Boston, Massachusetts
and HANS POPPER, M.D.
Department of Pathology
The Mount Sinai Hospital
New York, New York

[13] DAVIDSON, C. S. and PHILLIPS, G. B. Acute hepatic insufficiency in the chronic alcoholic; clinical and pathological study. *Arch. Int. Med.*, 94: 585, 1954.

[14] POPPER, H. and SZANTO, P. B. Fatty liver with hepatic failure in alcoholics. *J. Mt. Sinai Hosp.*, 24: 1121, 1957.

[15] POPPER, H., SZANTO, P. B. and PARTHASARATHY, M. Florid cirrhosis. *Am. J. Clin. Path.*, 25: 889, 1955.

Clinical Studies

The Effect of a Low Fat Diet on the Serum Lipids in Diabetes and Its Significance in Diabetic Retinopathy*

WILLIAM F. VAN ECK, M.D.
New Haven, Connecticut

NUMEROUS studies on the influence of dietary fat and cholesterol upon the different serum lipids have been published. It has become clear that a great many variables are involved and failure to take these into consideration presents many pitfalls in interpretation of the results. One must distinguish between short term effects, such as alimentary lipemia, and long-lasting effects, such as are found in the different mean serum cholesterol levels of populations with different dietary fat intakes [*1*]. Animal fat versus vegetable fats, the importance of unsaturated fatty acids and the relative distribution of carbohydrates and proteins are other variables [*2*], as are reducing diets [*3*] and the duration of starvation [*4*].

As an indicator of the serum lipid changes, the serum cholesterol has been used in the great majority of cases up to the present time [*5*]; more recently the serum lipoproteins have been employed for this purpose [*6–8*]. Neutral fat, especially in low fat diets, has received scant attention [*9,10*]. Excellent reviews discuss these and other problems of lipid metabolism at length [*2,11,12*].

It has been found that a diet low in fat results in a decrease of serum cholesterol [*9–11,13,14*] and possibly of certain fractions of the beta-lipoproteins [*7,9*]. Reduction of the dietary cholesterol alone is not very helpful [*1,11*]. A low fat diet gives a decrease of triglycerides in approximately 80 per cent of cases only if an ample protein intake is permitted; a rise, however, is found in 20 per cent [*9*]. Low protein-low fat diets result in erratic changes of serum triglycerides [*10*]. Administration of vegetable fat instead of animal fat lowers the serum cholesterol and the phospholipids [*15*]; this is probably owing to the unsaturated fatty acids which are present in vegetable fats [*2,16*]. Triglycerides do not show a consistent change when vegetable instead of animal fat is used [*2*].

The caloric balance also influences serum lipids in some way: a positive balance over a long period gives an elevation of the serum lipids but a doubled caloric intake in young men on a high fat diet is possible without such elevation if the excess energy is dissipated in physical exercise [*17*].

As compared with the abundant literature on the influence of dietary and other factors upon serum lipids, very little attention has been given to the significance of dietary fats for diabetes mellitus and its complications. When it was recognized early in the study of the disease that a disturbance in the utilization of carbohydrates was its main characteristic, prescribed diets contained a minimum of carbohydrates; the caloric balance was formed by fats. When insulin became available a more liberal intake of carbohydrates was permitted but fats still provided a considerable percentage of the daily food intake and the average diabetic diet at present contains from 80 to 110 gm. of fat daily [*18*].

It is a common clinical observation that atherosclerosis is more frequent in diabetic persons than in normal persons of the same age group [*19,20*]. Furthermore it is known that in poorly controlled diabetes all the serum lipids

* From the Departments of Pathology and Internal Medicine, Yale University School of Medicine, New Haven, Connecticut. This study was aided by research grant A-1165C from the National Institutes of Health, Public Health Service.

are increased [*21*]. Some authors, however, maintain that the serum lipids of properly controlled diabetes in patients taking the usual amount of dietary fats are normal [*22,23*]. Rabinowitch [*24*] stated, contrariwise, that diets low in fat and high in carbohydrates tended to decrease the serum cholesterol and might also prevent atherosclerosis. His diets, although considerably lower in fat than those generally used, still contained approximately 50 gm. of fat per day. The desirability of reducing the fat intake of diabetic subjects in certain clinical states has recently been discussed by Root [*25*]. Only one investigator, Singh [*26*], has described and advocated the use of a really low fat diet, but he mentioned no studies of the serum lipids nor were the effects of this program on diabetic retinopathy observed.

There are, however, a few incidental observations on the effects of a low fat diet in diabetes. Kempner, in 1945, during his studies on the effect of the "rice diet" in hypertensive disease, also observed patients with diabetes [*13*]. He noticed that they could be easily transferred to his low fat rice diet without requiring increased insulin and he described two cases in detail. In one the serum cholesterol dropped from 315 mg. per cent to 230 mg. per cent and a marked improvement of the retinopathy was noted. In the other patient no data on serum lipids were mentioned but considerable improvement of the retinopathy also was found. Similar results, but without details on fundi or serum lipids, were reported in three diabetic subjects by Watkin and co-workers in their extensive study of the significance of the rice diet in hypertension [*10*].

Nearly all serum lipid analyses reported in the literature have been made on the serum of fasting patients. Although this gives a good base line value it might obscure important changes in serum lipids occurring during the day. The high fat intake of most diabetic subjects can be expected to cause an elevation of triglyceride fat and cholesterol in the serum, and unless these daily fluctuations are recorded an incomplete picture of the behavior of the serum lipids will result. Failure to recognize the importance of such fluctuations might account for the opinions in the literature that deny the significance of fat intake for levels of the serum lipids in patients with diabetes.

The diurnal variation of serum lipids in diabetic patients was therefore studied and the effect of the daily fat intake on these patterns was observed over a period of six to twenty-four months. The patients were in caloric equilibrium during the observation period and their diabetes previous to the experimental diet was properly controlled so that only minimal glycosuria was permitted. The effect of lowering the fat intake on the course of the diabetic retinopathy was also observed. No chemical data are available on the composition of the retinal exudates commonly seen in diabetes but it seems possible that they contain lipids and that reduction of transported lipids in the serum might therefore affect their formation.

METHODS

All subjects had diabetes with retinopathy. Some were taking insulin; in others the disease was controlled by diet alone. (Table I.) All had been properly controlled, with infrequent slight glycosuria and no ketonuria for prolonged periods. Serial lipid studies were carried out in most cases, before starting the low fat diet, by examining blood samples at frequent intervals during the day. The patients were then requested to ingest a diet containing less than 20 gm. of fat daily (only the fat in the lean meat that they were permitted). The diet also contained 80 gm. of protein, and caloric equilibrium was maintained with carbohydrates to minimize changes in body weight. In most instances this meant the replacement of 80 to 110 gm. of fat by carbohydrates. Serial lipid studies were obtained three, six and twelve months after conversion to this diet in most cases. All patients were conscientiously observed to make sure that they followed the diet or to detect those who did not. Three admitted not having followed the diet as prescribed: one patient was seen to consume butter, eggs and milk freely, and he was dropped from the series; another admitted having neglected her diet; in the third case a private physician obtained this information although the patient had previously denied it. Before evidence of defection had been obtained, however, a rise in the serum lipids had aroused doubts about the reliability of these patients. Some of their lipid values have been included for comparison.

Although it was realized that our diet might interfere with the normal intake and absorption of fat-soluble vitamins, no dietary supplements of any kind were given.

Complete blood counts, hematocrit, urine, renal function (serum non-protein nitrogen, phenolsulphonphthalein excretion), serum electrolytes, serum proteins and liver function tests were performed at intervals during the study. Color photographs of the fundi were made of each patient before dietary treatment began and at three-month intervals thereafter. Total fatty acids were determined according to the method of Man and Gildea [*27*]; free cholesterol according to Sperry and Schoenheimer, as

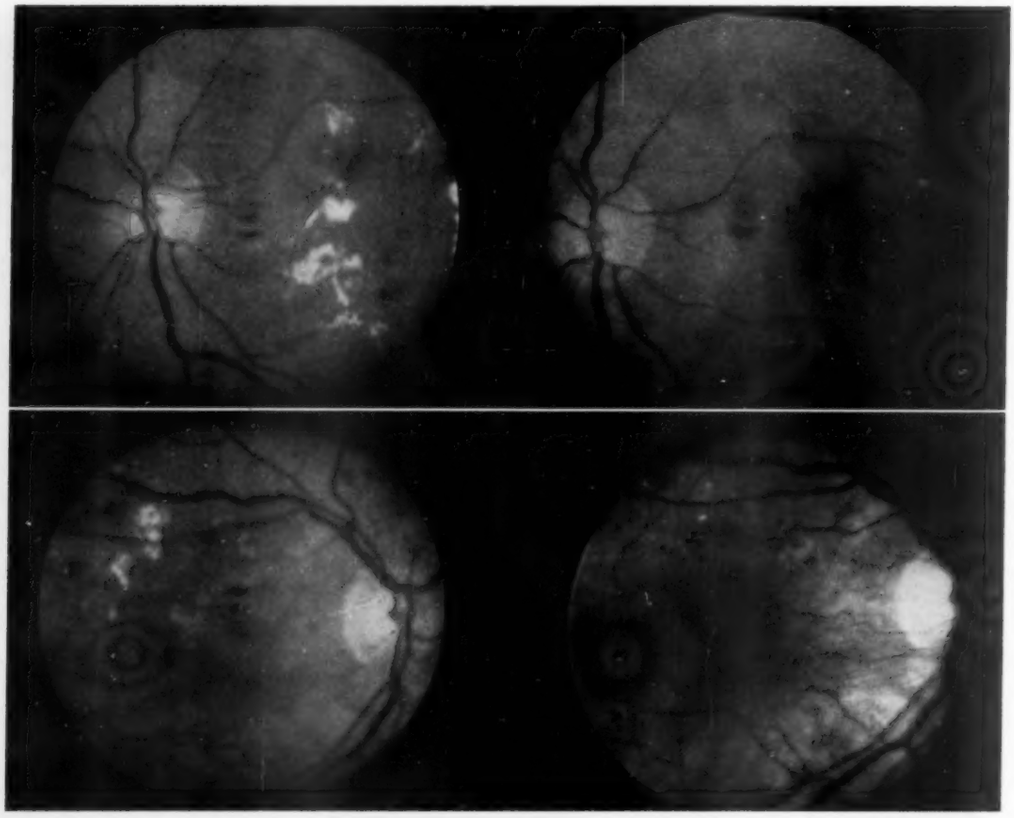


FIG. 1. Case I. Fundi of right and left eye before institution of a low fat diet (left) and fifteen months later (right).

modified by Sobel and Mayer [*28*]; total cholesterol according to Sperry and Brand [*29*]. Phospholipids were determined as lipid P according to Fiske and Subbarow [*30*].

The free and total cholesterol are calculated in milligrams per 100 ml. of serum; the fatty acids are expressed as milliequivalents per liter (normal limits, 5 to 20 mEq./L.) and the triglyceride fat is calculated as triglyceride fatty acids by subtracting the sum of cholesterol fatty acids and phospholipid fatty acids

TABLE I

DIABETIC HISTORY OF ALL CASES AND DAILY FAT INTAKE BEFORE THE EXPERIMENTAL DIET WAS STARTED

Patient and Case No.	Sex	Age at Onset of Diabetes (yr.)	No. of Years Patient was Diabetic	Minimum Number of Years of Retinopathy	Duration of Insulin Therapy (yr.)	Units of Insulin Per Day	Daily Fat Intake (gm.)
BN, I	F	34	35	?	10	50	80
BL, II	M	19	21	4	21	60	97
TR, III	F	58	4	4	0	0	80
TA, IV	F	36	20	1	2	30	100
IV, V	F	26	25	2	26	40	120
JH, VI	F	25	14	1	15	45	100
GN, VII	F	54	2	1	3	15	80
CO, VIII	F	62	2	1	0	0	100
TS, IX	F	42	13	2	1	20	75
WL, X	F	45	8	?	0	15	80
FT, XI	F	51	11	1	12	25	>100
ES, XII	M	47	3	1	0	10	>100

TABLE II

LABORATORY DATA BEFORE (1) AND AT THE END (2) OF THE LOW FAT DIET

Patient and Case No.	Low Fat Diet Started	Total Calories*	Weight (lb.)		Blood Pressure (mm. Hg)		Patency of Peripheral Arteries		Hemoglobin (gm. %)		Hematocrit (%)		Albuminuria		PSP† Excretion (%)		Serum Nonprotein Nitrogen (mg. %)		Albumin / Globulin (gm. %)	
			1	2	1	2	1	2	1	2	1	2	1	2	1	2	1	2	1	2
BN, I	Feb. 1954	1350	178	150	240/100	170/95	4/8	4/8	12	12.8	33	43	1+	1+	.. 15 9	.. .. ..	56	70	...	3.1/2.7
BL, II	June 1954	2260	148	...	200/130	185/120	5/8	5/8	12	....	40	..	4+	4+	5 20 20	.. .. ..	45	..	3.2/3.5	...
TR, III	Feb. 1955	2200	180	183	120/70	150/80	6/8	6/8	12	13	40	41	0	0	.. 35 10	30 20 10	59	37	3.5/2.7	3.4/3.1
TA, IV	April 1955	1800	161	153	155/75	160/80	4/8	2/8	13	11.5	34	35	1+	2+	19 20 12	18 15 5	44	39	2.1/2.8	1.7/2.8
IV, V	April 1956	2650	176	142	130/80	125/75	5/8	6/8	15	12	35	39	0	0	22 22 26	28 37 18	35	40	3.2/3.6	2.9/4.3
JH, VI	Sept. 1956	2500	112	112	135/90	140/85	7/8	7/8	14	14	..	45	0	0	.. 33	45 30 7 43	33	22	3.5/3.6	4.0/3.0
GN, VII	Oct. 1956	1450	147	133	160/90	170/90	6/8	6/8	14	12.1	41	42	0	0	11 11	34 10	33	31	3.0/3.6	4.0/2.3
CO, VIII	Nov. 1956	2000	128	111	200/80	250/120	3/8	3/8	11	12.4	33	38	1+	0	14 30 3	18 20 10	37	42	4.3/2.6	3.7/3.8
TS, IX	Dec. 1956	1450	141	139	120/80	125/80	6/8	6/8	14	12.2	42	36	1+	0	32 20 15	30 28 9	33	36	...	4.0/2.1
WL, X	Dec. 1957	1400	138	134	120/90	170/100	6/8	6/8	15	13.4	47	42	0	0	.. 63 18	.. 76 11	32	35	3.5/4.3	3.4/4.2
FT, XI	Mar. 1957	1400	145	145	150/90	195/85	...	...	15	15	..	48	0	0	.. 34	.. 45 5	29	46	4.3/3.4	3.5/3.0
ES, XII	Jan. 1957	2100	162	164	220/105	245/125	8/8	8/8	12.7	....	34	..	1+	1+	22 17	.. ..	36	..	2.7/3.4	...

* Total calories distributed in all cases: 80 gm. of protein, 10 to 20 gm. of fat. Balance: carbohydrates, except in Case XI (see text).

† Phenolsulfonphthalein.

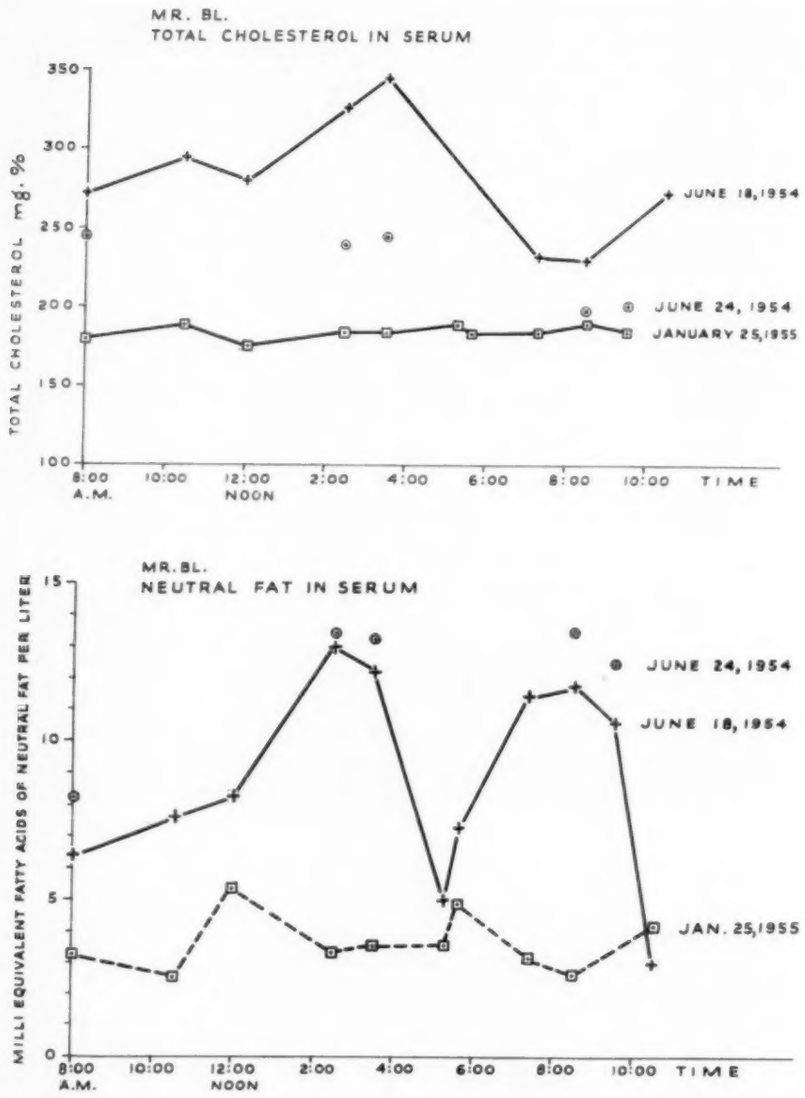


FIG. 2. Case II. Diurnal lipid curves before beginning the low fat diet and at intervals thereafter.

from total fatty acids [*23*] (normal limits, 3 to 10 mEq./L.).

RESULTS

Twelve patients, ten women and two men, were followed up for various periods of time between 1954 and 1957; seven of them are still under observation at the time of writing. Of the remaining five subjects, two have died, two did not care to continue the diet, and one withdrew from treatment. Of the original group eleven continued the low fat diet faithfully for periods of six months to two years.

The date of onset of diabetes as well as of retinopathy is nearly always uncertain, because both diseases may exist for several years without subjective symptoms. Our estimates of duration are therefore only approximate. The majority of the subjects had had diabetes for more than ten years (Table 1) but there were two patients whose diabetes had been recognized for only three years who nevertheless had very marked diabetic retinopathy. All patients had previously been on the usual high fat diet. Nearly all had had 100 gm. or more of fat per day, and in the two patients who claimed a lower fat intake, it was evident on questioning that in preceding years they had eaten more fat.

TABLE III
SERUM LIPIDS OF PATIENT BNDCT.

Date	Serum Cholesterol		Serum Lipid P (mg. %)	Serum Total Fatty Acids (mEq./L.)	Serum Neutral Fat Fatty Acids (mEq./L.)
	Total (mg. %)	Free (mg. %)			
2/12/54	292	93	9.7	19	8.2
4/2/54	223	63	10.4	20	9.9
11/15/54	253	69	11.4	19	7.6
6/22/55	176	50	8.2	7.3	0
7/14/55	165	44	8.6	13	4.9
12/3/55	126	34	6.6	7.3	1.1

Four patients had hypertension. Most showed signs of peripheral arteriosclerosis but it was difficult to evaluate this precisely. In Table II we have tried to give some quantitative expressions to the degree of arteriosclerosis by determining the number of peripheral arteries of arms and legs (radial, ulnar, posterior tibial and dorsal pedal) in which a pulse could be palpated; 3/8, for instance, means that three of the eight arteries mentioned were patent and five occluded. Four patients had mild anemia. Albuminuria was present in four; renal function was satisfactory in most patients but in two of them (Bl and Bndct) there was terminal elevation of the blood non-protein nitrogen. The serum proteins in most cases showed an elevated globulin with a decrease in albumin.

There was no important change in the clinical and laboratory findings of any patient during the period of observation and low fat diet with the exception of the rise in blood non-protein nitrogen in two patients. All but two maintained their body weight by exchanging the fats in their diet for carbohydrates. The replacement of 100 gr. of fat with carbohydrates was possible in all cases without raising the amount of insulin, by first withdrawing the fats and then permitting gradually increased amounts of carbohydrates. This surprising increase in glucose tolerance was also seen in the two patients who were not taking insulin and who therefore consumed up to 400 gr. of carbohydrates without requiring any. The effects of the diet on the serum lipids and the retinal changes observed will be described in detail for each patient.

CASE REPORTS

CASE I. Mrs. Bndct., a sixty-nine year old woman who had had diabetes for thirty-five years, had severe retinopathy with large exudates. At the beginning of

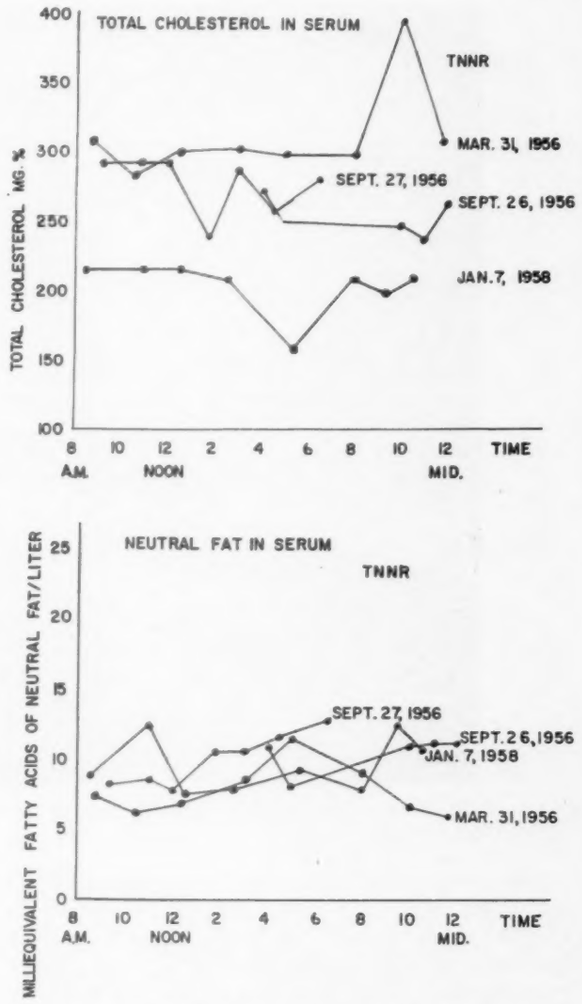


FIG. 3. Case III. Diurnal lipid curves before beginning the low fat diet and at intervals thereafter.

the clinical observation (Table III) her serum total cholesterol was 292 mg. per cent and the triglycerides 8.2 mEq./L. She started the low fat diet in February 1954 and during the next two years her serum lipids slowly decreased. Serial lipid studies during twenty-four-hour periods were unobtainable and her lipids represented fasting specimens. There can, however, be no doubt about the marked drop in serum lipids during the time of observation. The very low values obtained in December 1955 may be due to semi-starvation in her final months of life. She died of cardiac failure shortly thereafter. Photographs of the fundi showed a great reduction in the size of the exudates. Two years later the fundi were nearly clear. (Fig. 1.) This disappearance of the exudates occurred very slowly, the first changes becoming visible only after three to six months of dieting.

CASE II. Mr. Bl., forty-two years old, was totally blind, with irreparable changes in both eyes when he

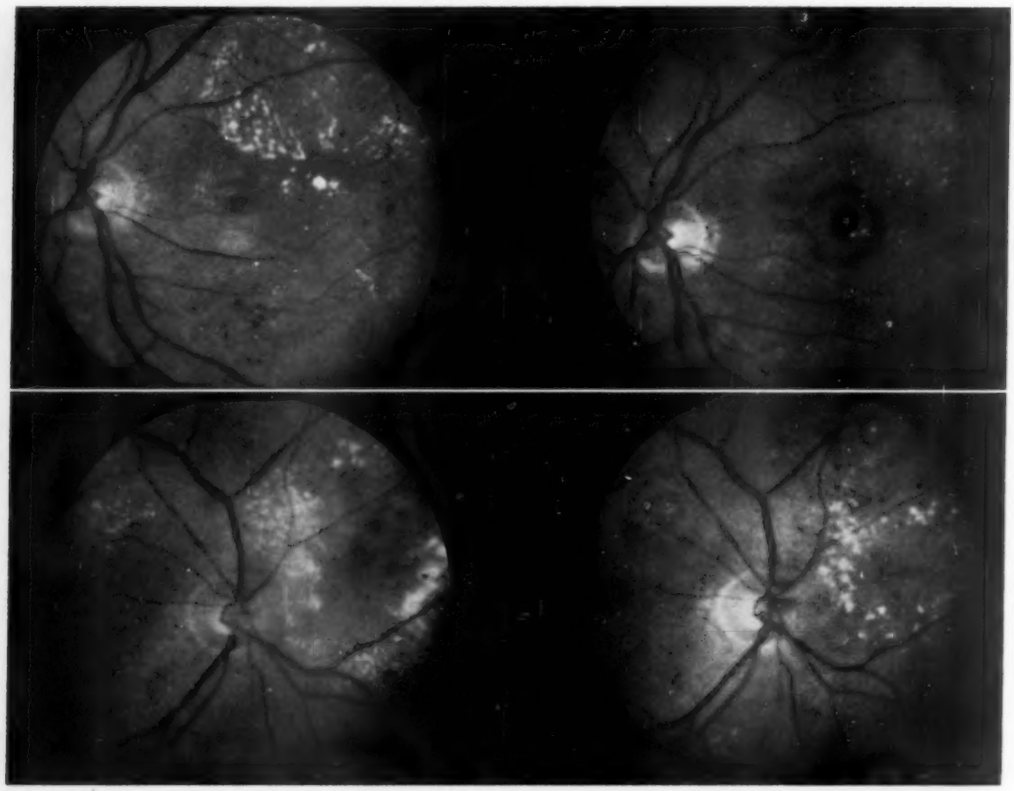


FIG. 4. Case III. Fundi of right and left eye before institution of a low fat diet (left) and five months later (right).

was first seen. His diabetes had always been carefully controlled. However severe retinopathy and Kimmelstiel-Wilson syndrome developed. He had marked peripheral arteriosclerosis, hypertension and reduced renal function. (Table II.) A low fat diet was instituted on June 19, 1954. Serial lipid studies during the day were made before this diet, one week after starting the diet, and seven months later. The values for serum total cholesterol and triglycerides are presented in Figure 2. Of special interest are the marked fluctuations in both triglyceride fat and cholesterol during the day. Note that after the patient had been on the low fat diet for one week the serum cholesterol and triglycerides were still clearly elevated, the last fraction showing high values at the same time of day as before. However, half a year later a considerable drop of the serum lipids was found and the values throughout the day plot out as a nearly horizontal line. Because the patient lived out of the state only incidental follow-up studies could be made, which showed little change. He died a year and a half later from cerebral hemorrhage.

CASE III. Mrs. Tnnr., sixty-two years old, had marked diabetic retinopathy with large exudates in both fundi. She did not use insulin with her regular diet or while on the low fat diet. Her serum lipids were only mildly elevated. During the first period of observation they were drawn once a month at 1:00 P.M. A slight drop was observed during that period, from an average of 250 mg. of total cholesterol to 220 mg. and 14 mEq./L. of triglycerides to 7 mEq./L. After one year the patient was given a high fat diet (more than 100 gr. of fat daily) which was continued from February to September 1956. After that the patient resumed the low fat diet (less than 20 gr. daily) A slight drop in serum cholesterol occurred promptly and four months later the serum total cholesterol had dropped from a fluctuating 300 to 400 mg. per cent to a level of 200 mg. per cent. Little change had occurred in the neutral fat fraction of this patient. (Fig. 3.) The eyegrounds showed remarkable changes. During the first year of the low fat diet the large exudates almost completely disappeared. (Fig. 4.) Following reinstitution of the high fat diet new exudates developed, although after a considerable time lapse. They subsequently disappeared again when the fats were withdrawn.

CASE IV. Mrs. Tnna., fifty-six years old, had had diabetes for twenty years. Minimal retinopathy, consisting of small groups of tiny exudates, had been discovered recently. She also had a mild form of Kimmelstiel-Wilson syndrome. (Table II.) Her fasting lipids were elevated, the serum total cholesterol at one time being above 500 mg. per cent. Two months after

she started the low fat diet, a marked drop of the serum lipids was obtained. The patient then began eating fats again and the serum cholesterol rose to previous high values, to drop again under closer supervision. Concomitantly her serum triglycerides decreased somewhat. The values are of limited significance because the patient admitted to frequent lapses in her diet and refused to stay on any diet after a trial period of eight months. Thereafter her serum cholesterol again rose to high values (500 mg. per cent). A decrease in the number and size of the exudates was observed during the period of the low fat diet. One year later numerous large exudates had formed. This coincided with poor control of her diabetes and chronic heart failure.

Case v. Mrs. Ivs., fifty-one years old, had had diabetes for twenty-five years and retinopathy for two years. Vascular abnormalities were preponderant in both eyegrounds, but she also had some exudates. No indication of Kimmelstiel-Wilson syndrome was apparent. After beginning her low fat diet the serum cholesterol dropped approximately 25 per cent and remained at the lower level for a year and a half. The serum triglyceride fat fraction, which was not elevated to begin with, remained unchanged. Serial lipid studies during the day at the beginning and end of this experimental period are shown in Figure 5. Photographs of the fundi showed disappearance of all small exudates of the left eye in eight months; the changes in the right eye during the last half year could be seen. The circle of minute exudates around the macula developed while the patient was on the low fat diet, probably after a hemorrhage, and disappeared subsequently. (Fig. 6.) In this patient the vascular disease of both eyes continued unabated for two years and she had several hemorrhages resulting in proliferative retinitis and decrease of eyesight. The discrepancy between vascular abnormalities and the development of exudates has been noticed to a lesser degree in other patients.

Case vi. Miss Jhns., a thirty-eight year old woman had had diabetes for fourteen years, and a mild retinopathy for one year. Her serum cholesterol fractions were markedly elevated (total cholesterol 300 to 350 mg. per cent) but her triglyceride fat was normal. Following institution of the low fat diet the serum total cholesterol dropped to 200 mg. per cent or below, as illustrated in two daily curves with an eight-month interval. (Fig. 7.) These low values have been maintained for two years. The diabetic retinopathy cleared. In the course of the first year all exudates disappeared; some microhemorrhages recurred but were absorbed without apparent damage.

Case vii. Mrs. Gndy., fifty-six years old, had had diabetes for two years with marked retinopathy including numerous large exudates. In the

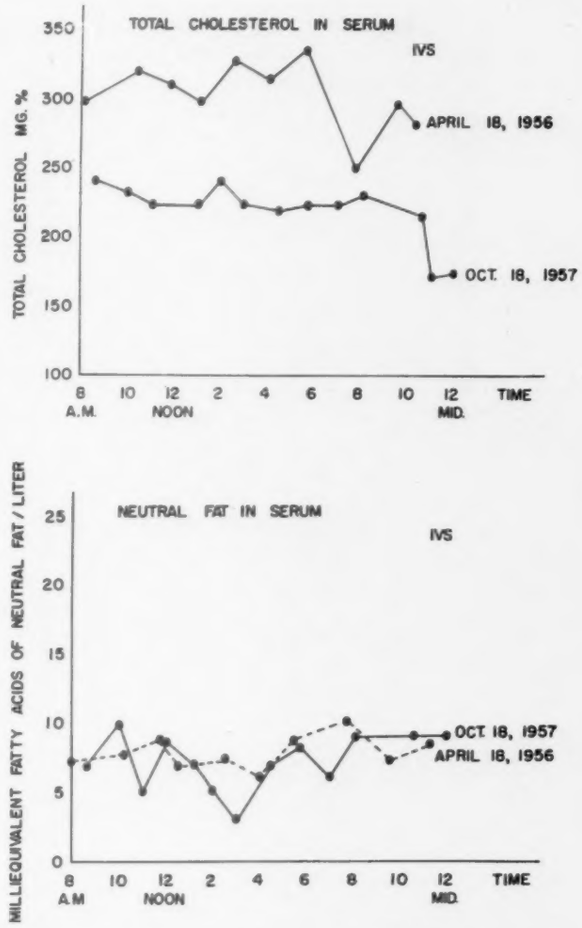


Fig. 5. Case v. Diurnal lipid curves before beginning the low fat diet and six months thereafter.

right fundus, halfway between the papilla and macula, an especially large mass of exudate was present, quite prominent above the level of the retina and apparently protruding into the vitreous body. Following institution of the low fat diet the behavior of her serum lipids was especially interesting when compared with the previous case. The serum triglyceride fraction showed the largest drop, although a decrease in serum total cholesterol also was observed. (Fig. 8.) At the same time a marked decrease in the size and number of exudates all through the fundus was noticed and even the previously described mass diminished slowly in size.

Case viii. Mrs. Cork, sixty-four years old, had had diabetes for two years and extensive retinopathy with a multitude of small exudates and many small retinal hemorrhages in both fundi. The serum lipids were markedly elevated. Both serum cholesterol fractions and the triglyceride fat dropped to normal levels following institution of the low fat diet. (Fig. 9.) The eyegrounds returned to normal in the course of one

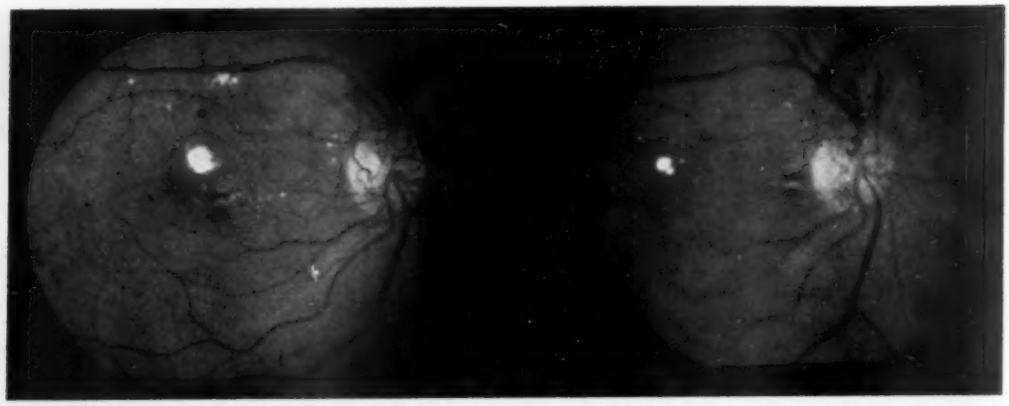
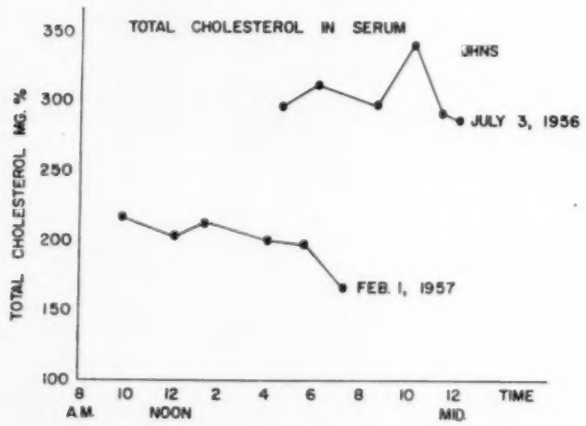
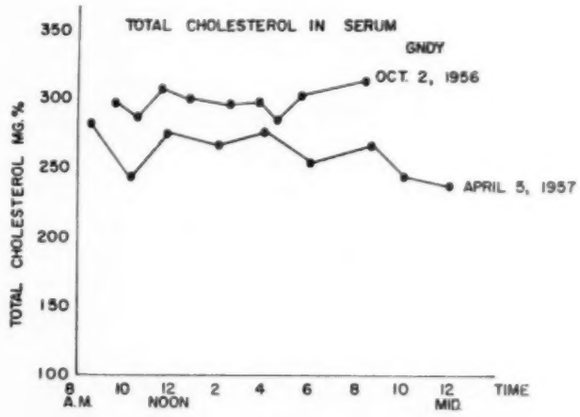


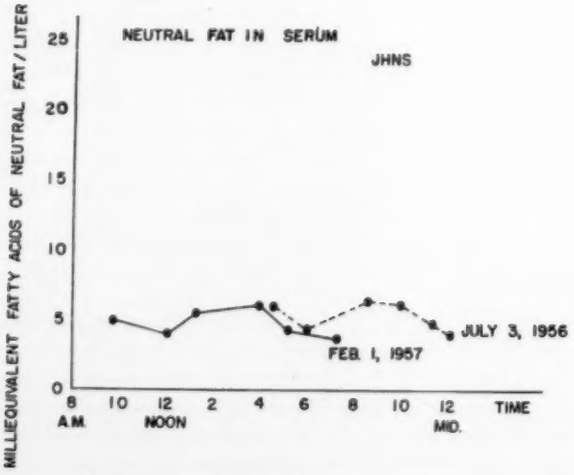
FIG. 6. Case v. Fundus of right eye before institution of a low fat diet (left) and eight months later (right).

year. (Fig. 10.) During the last months of this year her fat intake increased and the serum lipids rose. After resuming the strict low fat diet a rapid drop in serum lipids occurred.

CASE IX. Mrs. Tscll., a fifty-five year old woman who had had diabetes for thirteen years, showed mild retinopathy. Her serum cholesterol was elevated, approximately 300 mg. per cent. During the year that she followed the low fat diet this decreased to







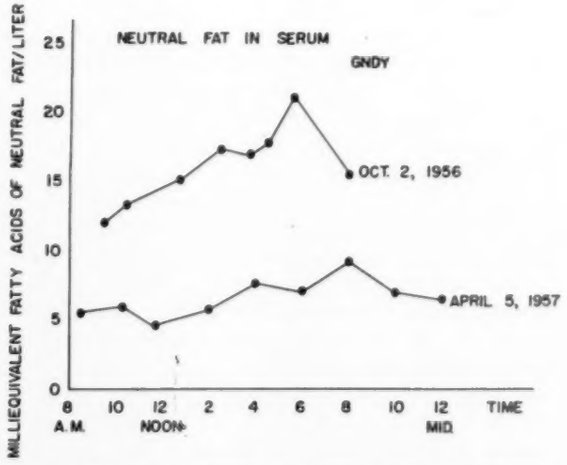


FIG. 7. Case VI. Diurnal lipid curves before beginning the low fat diet and seven months later.

FIG. 8. Case VII. Diurnal lipid curves before beginning the low fat diet and six months thereafter.

almost 200 mg. per cent. The triglyceride fat, if anything, increased slightly but remained below 10 mEq./L. The exudates in the right eye decreased during the first seven months. The left eye had a small retinal hemorrhage in December 1956 when she began the low fat diet. Three months later the hemorrhage had disappeared but in its place was a deposit of white material which subsequently disappeared during the next four months. (Fig. 11.)

CASE X. Mrs. Wlls., a fifty-three year old woman who had had diabetes for eight years, presented a very mild retinopathy. Her serum lipids were within the normal range, the total cholesterol fluctuating throughout the day at approximately 250 mg. per cent. After starting the low fat diet her serum total cholesterol dropped to below 200 mg. per cent which was maintained for more than a year. A group of exudates in both eyes disappeared but in the right eye a circle of tiny new exudates appeared, perhaps in the wake of a hemorrhage. Similar new exudates in the left eye seemed to be related to previously observed hemorrhages. The larger exudates in the left fundus almost completely disappeared.

CASE XI. Miss Fte., sixty-two years old, had had diabetes for eleven years and retinopathy for at least one year. Her serum total cholesterol was elevated, around 300 mg. per cent, and the triglyceride fat varied from 5 to 11 mEq./L. In the first two months of diet there was a slight fall in the serum cholesterol but a serial curve five months later again showed high values, above 300 mg. per cent. There was no improvement of the retinopathy. Miss Fte. finally acknowledged that she did not follow the low fat diet at all after the first few months and this failure is reported because it stresses the difficulty of being certain whether a patient follows a difficult diet without close supervision. Her case is also reported as a control study to show the persistence of the lipid pattern in a patient who remains on the usual fat intake.

CASE XII. In Mr. Esp., a fifty year old man who had had diabetes for three years with extensive retinopathy, the Kimmelstiel-Wilson syndrome also developed with marked hypertension. (Table II.) The patient was admitted with an acute appendicitis with complications, and the base line values for his serum lipids were therefore obtained after he had already followed a low fat diet for two months. His serum total cholesterol was 298 mg. per cent and triglycerides 10 mEq./L. Subsequent serum analyses one and five months later showed a serum total cholesterol of 247 and 243 mg. per cent and triglycerides of 4.9 and 3.6 mEq./L., respectively. The patient refused further blood studies and only one set of repeat photographs of the fundus could be obtained, approximately six months after he started the low fat diet. (Fig. 12.) A marked reduction of the exudates was noticeable.

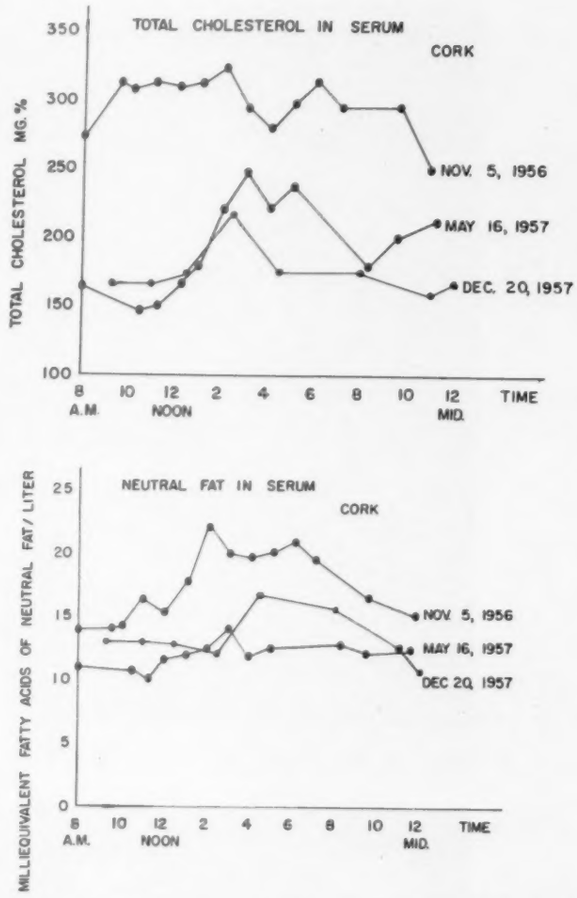


FIG. 9. Case VIII. Diurnal lipid curves before beginning the low fat diet and at intervals thereafter.

COMMENTS

Many authors in the past have observed that an increase in the ingestion of carbohydrates was followed by increased carbohydrate utilization [*31*] which continued even after insulin therapy was withdrawn [*32*]. In the presence of a high carbohydrate intake a change in the fat content of the diet did not appear to affect carbohydrate tolerance [*32,33*]; however in all these studies the minimum fat intake was apparently more than 40 gm. per day.

Our results are in close agreement with the incidental findings of Kempner's rice diet-hypertension studies [*13*], later corroborated by Watkin and colleagues [*10*]. Their diet was different from ours in that we permitted at least 80 gm. of protein while the rice diet had 20 to 30 gm. of protein and was also very low in salt. Since both high protein-low fat and low protein-low fat diets as well as our low fat-high carbohydrate-average protein diet have resulted in unchanged

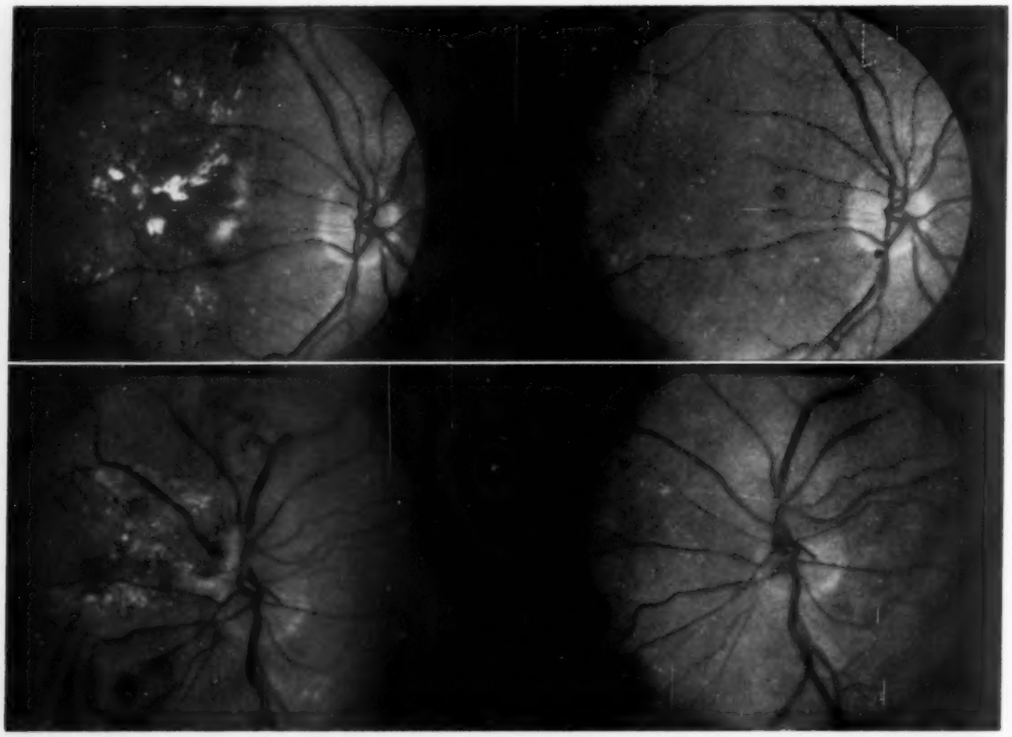


FIG. 10. Case IX. Fundi of right and left eye before institution of a low fat diet (left) and one year later (right).

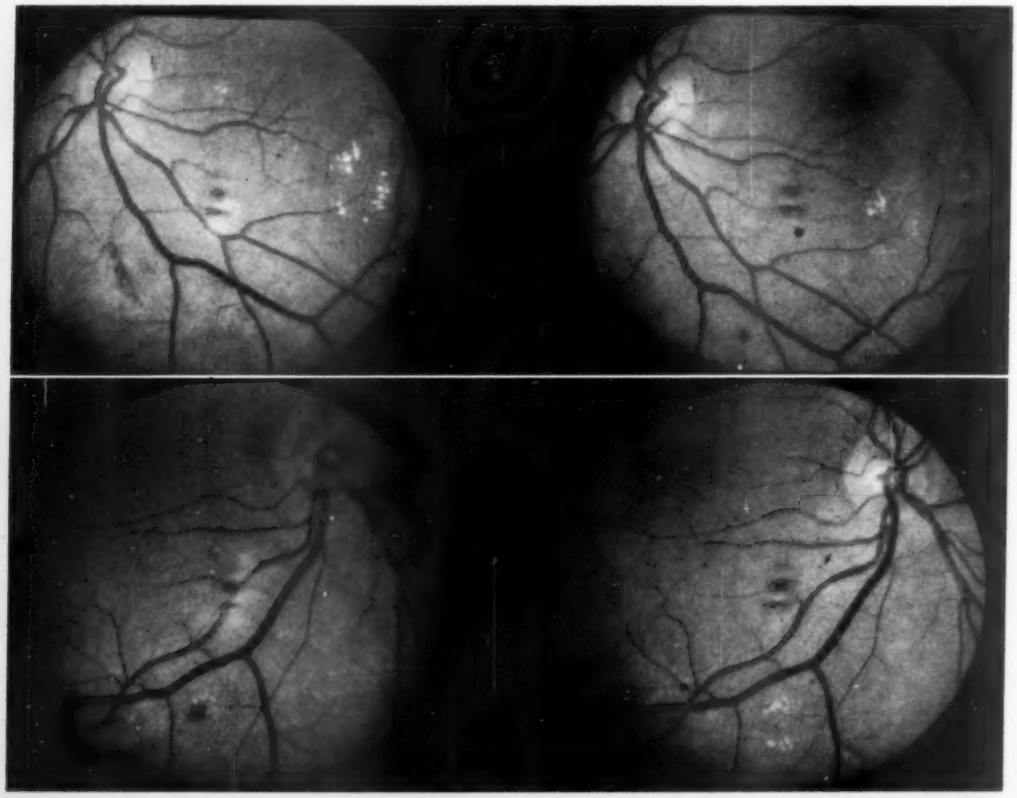


FIG. 11. Case IX. Fundi of right and left eye before institution of a low fat diet (left) and eight months later (right). Note the disappearance of the small hemorrhage and the residual exudate in the lower pair of photographs.

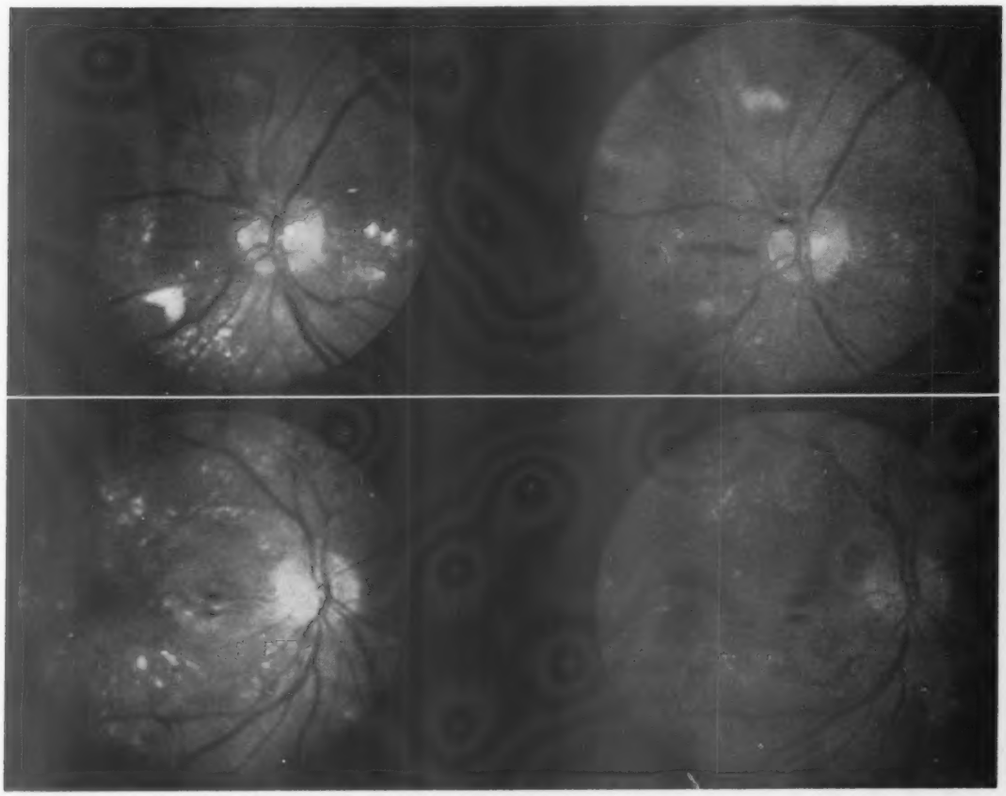


FIG. 12. Case XII. Fundi of right and left eye before institution of a low fat diet (left) and six months later (right).

or even decreased insulin requirements, it follows that either the reduction of fats or the increased amount of carbohydrates in the diet was responsible for the increased glucose tolerance in these diabetic patients.

All our subjects tolerated an increase of at least 135 gm. of carbohydrates without increasing the amount of insulin, and the same change in diet could be obtained in patients who did not require insulin. The mechanism of this phenomenon is not clear, but one can speculate that the low fat-high carbohydrate diet diminishes the fat deposits in the liver and improves glucose oxidation.

Due to limitations of space, it is not possible to report the hundreds of analyses made to show the variations of serum lipids in our patients on low fat diets. In lieu of these the graphs illustrating diurnal changes in serum total cholesterol and triglyceride fat, before and during the low fat diet, may give a sufficient idea of the variations observed.

The serum free cholesterol and cholesterol ester fractions changed more or less proportionally although the cholesterol esters comprised a slightly lower percentage of the total cholesterol than has been reported for normal persons. An illustration of the parallel changes of total and esterified cholesterol is given in Figure 13.

In order to summarize the percentage change during the low fat diet, averages of monthly lipid analyses of all patients, expressed as percentages of the base line values for serum total cholesterol, were compiled. (Fig. 14.) Those patients who initially had little elevation in serum total cholesterol reduced the percentage of reduction in total serum cholesterol disproportionately. Nevertheless an average drop of about 20 per cent is obtained and persists throughout the period of observation. This composite graph refers only to single monthly analyses, in contrast to the diurnal graphs. Furthermore the pretreatment value of each patient was compared with the value obtained after three months of treatment and the decrease in each case is represented in Figure 15. For convenience the cases have been arranged in order of their pretreatment levels of serum total cholesterol.

One patient, after having followed the low fat diet faithfully for several months, was found to have increased her dietary fat intake. Reinstitu-

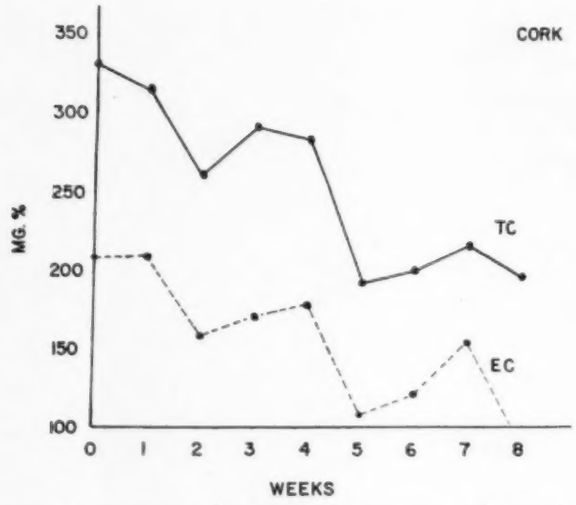


FIG. 13. Case VIII. Weekly fall in serum cholesterol. Weekly analyses demonstrate the effect of the low fat diet on the serum cholesterol of this patient. Note the parallel changes of serum total and esterified cholesterol.

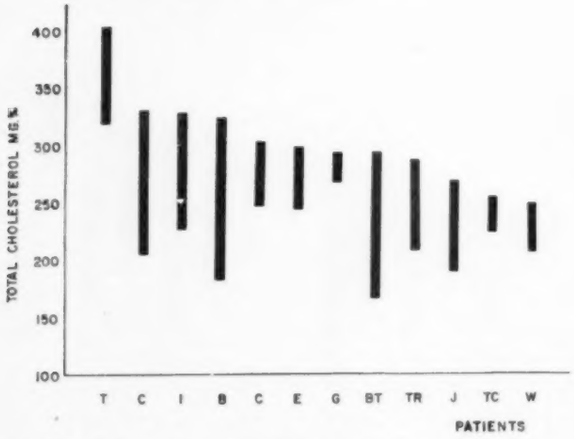


FIG. 15. Fall in serum cholesterol in each case. Each bar represents the fall in serum cholesterol during the first three months of the low fat diet in each case. Case C (Cork) is represented twice (see text).

tion of the strict diet was promptly followed by a renewed drop of her serum lipids; the changes obtained by weekly analyses are illustrated for total and esterified cholesterol in Figure 13. The importance of including diurnal series of lipid analyses in these cases has already been stressed and reported results have clearly supported this view, even if not all patients showed well defined alimentary peaks; this may be due to overlapping absorption from the different meals while the patients were on a high fat diet. From the graphs and other data we can conclude that diabetic patients who have either elevated serum cholesterol or triglyceride fractions, when transferred to a low fat diet, will show a reduction of whatever lipid fraction was elevated.

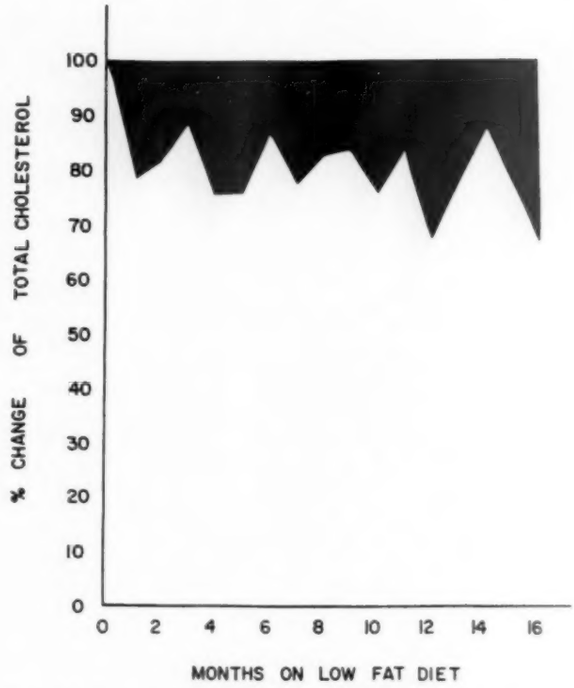


FIG. 14. Percentage fall in serum cholesterol of all cases combined. This curve represents the average monthly fall in serum cholesterol in all cases, expressed as percentage of the pretreatment level.

In all patients who adhered to the low fat diet the reduced serum lipid levels were maintained for the duration of the observation; in some cases more than two years. When no drop in serum lipids occurred or a subsequent rise was observed, it could be established that the patient had not adhered to the diet.

There is evidence of some correlation between triglycerides and glycemia. In non-diabetic healthy persons, Albrink [*34*] has demonstrated that the hyperlipemia which followed ingestion of 60 gm. of fat could be prevented by ingestion of 100 to 250 gm. of carbohydrates. For diabetic subjects this correlation has been described by Hirsch [*35*]. In our diabetic patients we found no evidence that glycemia, under the conditions of the diet, influenced the serum lipids (Fig. 16); considerable fluctuation of the blood sugar during the day occurred with a flat lipid curve. One patient (Tnna.) repeatedly had varying blood sugars with persistently high serum lipids. A low fat diet could still give a considerable rise in triglycerides of the serum if all the ingested lipids remained in circulation for a few hours. A difference in triglycerides of, say, 15 mEq./L. cor-

responds to only 12.8 gm. of triglyceride fat in 3 L. of serum. Apparently rapid deposition of fat occurs. Similarly, a low fat diet cannot affect the level of serum lipids merely through the lesser absorption of fat. This is obvious from the time required to reduce the serum lipids, which in our patients was several weeks. It seems therefore that the amount of ingested and absorbed fat itself plays a part in regulating the maintenance of serum lipid levels.

The laboratory tests of our patients before and during the dietary period showed little change. (Table II.) The results of the liver function tests have not been included in this table since they remained entirely normal. We have no reason to suspect, therefore, that our diet caused any liver damage during the period of observation.

While the diabetic patients were ingesting the low fat diet, changes in their retinae were observed which have been documented by black and white reproductions of Kodachromes. Diabetic retinopathy has two major components: vascular abnormalities (microaneurysms and hemorrhages) and the so-called exudates. Whatever their composition, these exudates are obviously due to passage of material from the small vessels. We have photographic evidence that they can develop in the wake of a hemorrhage (Fig. 11) but hemorrhages can disappear without leaving white exudates and they may form without a preceding hemorrhage; also, they do not all look alike and they may have a variable genesis and composition. Their natural history is not sufficiently known; small ones may come and go, but the disappearance of large ones that have developed in properly controlled diabetic patients is rare. Careful observation of the changes of these exudates in patients with diabetes, without specific treatment, is necessary for a better evaluation of our results.

With these reservations in mind we observed in eight of our ten patients, who had retinopathy with exudates, that regression of the exudates occurred. In two patients large exudates, up to several times the diameter of the optic disc, disappeared (Bndct., Tnnr.); in three patients agglomeration of many small exudates disappeared or decreased considerably in size and number (Cork, Gndy., Esp); in three who had few exudates to start with, the changes were more discrete but still clearly evident. In two patients the regression was not convincing, mostly because of the formation of tiny new exudates while the patient was on the low fat diet

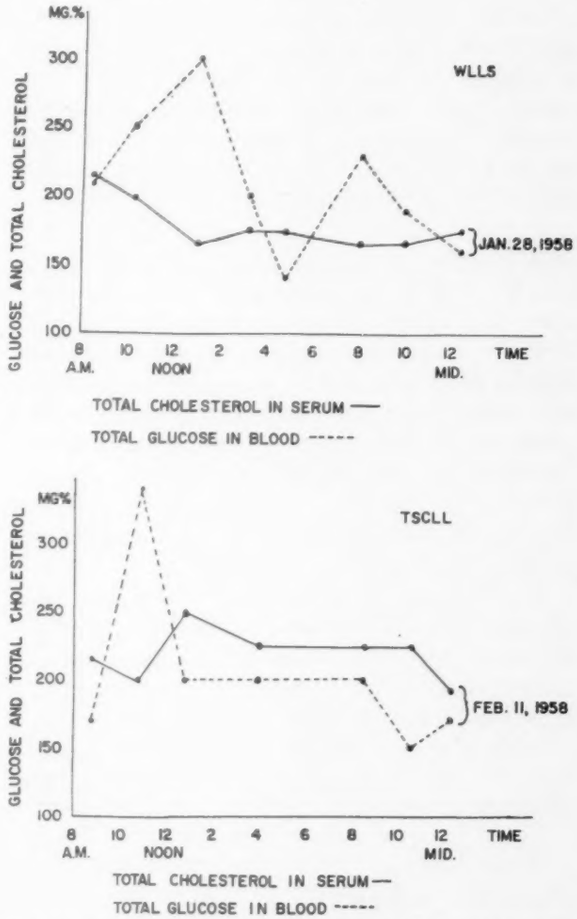


FIG. 16. Case IX (Tscll.) and X (Wlls.). Diurnal glucose and cholesterol curves. In both cases lack of correlation between diurnal values of glucose and cholesterol is seen.

(Tscll., Wlls.). Together with disappearance or reduction of the exudates, improvement of the retinal angiopathy was observed in one patient; this, however, was the exception and in most cases the vascular disease continued to manifest itself by microaneurysms and hemorrhages. While we do not postulate any immediate or indirect effects of the low fat diet on diabetic retinopathy we should like to draw attention to such a possibility.

On the basis of the information so far obtained, it seems justifiable to consider a strict low fat diet for diabetic patients who have elevated serum lipids and distinct retinopathy.

SUMMARY AND CONCLUSIONS

1. The effect of a diet containing only 20 gm. of fat per day was studied in a group of twelve patients with diabetes with retinopathy and elevated serum lipids.

2. We observed a striking increase in the glucose tolerance of these patients, which made it possible to increase the carbohydrates to at least 135 gm. per day, without increase of the insulin requirement. Patients who were controlled by diet alone did not require insulin after the transition to the low fat diet.

3. Of the eleven patients who followed this diet, lowering of the serum lipids was obtained in ten. This effect was maintained during the entire observation period of one to two years.

4. Of the ten patients who presented exudates in their fundi, marked decrease or disappearance was noticed in five; discrete but convincing reduction in three others. In two patients, whose exudates were minimal to start with, the changes were less convincing. In no patient who followed the low fat diet did new large exudates develop during the observation period.

5. Although no immediate or indirect relationship has been proved to exist between the observed lowering of the serum lipids and the disappearance of retinal exudates, such a relationship is suggested for further study.

6. It seems justifiable to consider a strict low fat diet in diabetic patients who present elevated serum lipids and distinct retinopathy.

Acknowledgment: The kindness of Dr. Levin Waters in making available the facilities of his laboratory for this work is deeply appreciated. Photographs of the fundi were kindly made by Dr. Ernest Rosenthal, Department of Ophthalmology.

REFERENCES

1. Keys, A. Human atherosclerosis and diet. *Circulation*, 5: 115, 1952.
2. Ahrens, E. H., Jr. Nutritional factors and serum lipid levels. *Am. J. Med.*, 23: 928, 1957.
3. Moore, N. S., Young, C. M. and Maynard, L. A. Blood lipid levels as influenced by weight reduction in women. *Am. J. Med.*, 17: 348, 1954.
4. Kartin, B. L., Man, E. B., Winkler, A. W. and Peters, J. P. Blood ketones and serum lipids in starvation and water deprivation. *J. Clin. Invest.*, 23: 824, 1944.
5. Proceedings of the eleventh annual meeting of the American Society for the Study of Arteriosclerosis. *Circulation*, 16: 479, 1957.
6. Gofman, J. W., Lindgren, F. T. and Elliot, H. Ultracentrifugal studies of lipoproteins of human serums. *J. Biol. Chem.*, 179: 973, 1949.
7. Walker, J., Weiner, N. and Milch, L. J. Differential effect of dietary fat and weight reduction on serum levels of beta-lipoproteins. *Circulation*, 15: 31, 1957.
8. Havel, R. J. Early effects of fasting and of carbohydrate ingestion on lipids and lipoproteins of serum in man. *J. Clin. Invest.*, 36: 855, 1957.
9. Hatch, F. T., Abell, L. L. and Kendall, F. E. Effects of restriction of dietary fat and cholesterol upon serum lipids and lipoproteins in patients with hypertension. *Am. J. Med.*, 19: 48, 1955.
10. Watkin, D. M., Froeb, H. F., Hatch, F. T. and Gutman, A. B. Effects of diet in essential hypertension. II. Results with unmodified Kempner rice diet in fifty hospitalized patients. *Am. J. Med.*, 9: 428, 1950.
11. Keys, A., Anderson, J. T., Nickelsen, O., Adelson, S. F. and Fidanza, F. Diet and serum cholesterol in man. *J. Nutrition*, 59: 39, 1956.
12. Zilversmit, D. B. Current concepts of lipide metabolism. *Am. J. Med.*, 23: 120, 1957.
13. Kempner, W. Compensation of renal metabolic dysfunction. Treatment of kidney disease and hypertensive vascular disease with rice diet. III. *North Carolina M. J.*, 6: 117, 1945.
14. Urbach, F., Hildreth, E. A. and Wackerman, M. T. The therapeutic uses of low fat, low cholesterol diets. *J. Clin. Nutrition*, 1: 52, 1952.
15. Kinsell, L. W. Effects of high-fat diets on serum lipids. *J. Am. Diet. A.*, 30: 685, 1954.
16. Kinsell, L. W. and Michaels, G. D. Letter to the editor. *Am. J. Clin. Nutrition*, 3: 247, 1955.
17. Mann, G. V., Teel, K., Hayes, O., McNally, A. and Bruno, D. Exercise in the disposition of dietary calories. *New England J. Med.*, 253: 349, 1955.
18. Joslin, E. P. et al. The Treatment of Diabetes Mellitus, 8th ed., p. 259. Philadelphia, 1948. Lea & Febiger.
19. White, P. Diabetes in youth. *New England J. Med.*, 224: 586, 1941.
20. Dolger, H. Factors influencing premature cardiovascular degeneration in diabetes mellitus. In: Progress in Clinical Endocrinology. Edited by Soskin, S., pp. 303–306. New York, 1950. Grune & Stratton.
21. Bloor, W. R. The lipoids ("fats") of the blood in diabetes. *J. Biol. Chem.*, 26: 417, 1916.
22. Man, E. B. and Peters, J. P. Serum lipoids in diabetes. *J. Clin. Invest.*, 14: 579, 1935.
23. Peters, J. P. and Van Slyke, D. D. Quantitative Clinical Chemistry, vol. 1, pp. 509–510. Baltimore, 1946. Williams & Wilkins Co.
24. Rabinowitch, I. M. Arteriosclerosis in diabetes. *Ann. Int. Med.*, 8: 1436, 1935.
25. Root, H. F. Diabetes Mellitus. New York, 1956. Landsberger Medical Books.
26. Singh, I. Low-fat diet and therapeutic doses of insulin in diabetes mellitus. *Lancet*, 1: 422, 1955.
27. Man, E. B. and Gildea, E. F. The effect of the ingestion of a large amount of fat and of a balanced meal on the blood lipids of a normal man. *J. Biol. Chem.*, 99: 61, 1932.
28. Sobel, A. E. and Mayer, A. M. Improvements in the Schoenheimer-Sperry method for the determination of free cholesterol. *J. Biol. Chem.*, 157: 255, 1945.
29. Sperry, W. M. and Brand, F. C. The colorimetric determination of cholesterol. *J. Biol. Chem.*, 150: 315, 1943.
30. Fiske, C. H. and Subbarow, Y. The colorimetric

determination of phosphorus. *J. Biol. Chem.*, 66: 375, 1925.

31. STROUSE, S. and SOSKIN, S. Treatment of the same diabetic patient with widely varying diets. *Tr. A. Am. Physicians*, 47: 317, 1932.
32. MIRSKY, I. A., FRANZBLAU, A. N., NELSON, N. and NELSON, W. Role of excessive carbohydrate intake in etiology of diabetic coma. *J. Clin. Endocrinol.*, 1: 307, 1941.
33. WATSON, E. M. and WHARTON, M. A. A comparison of various diets in the treatment of diabetes mellitus. *Quart. J. Med.*, 4: 277, 1935.
34. ALBRINK, M. J., FITZGERALD, J. R. and MAN, E. B. Reduction of alimentary lipemia by glucose. *Metabolism*, 7: 162, 1958.
35. HIRSCH, E. F., PHIBBS, B. P. and CARBONARO, L. Parallel relation of hyperglycemia and hyperlipemia in diabetes. *Arch. Int. Med.*, 91: 106, 1953.

The Effects of Fasting and Diabetes Mellitus on Myocardial Metabolism in Man*

WALTER T. GOODALE, M.D., ROBERT E. OLSON, M.D.,† *and* DONALD B. HACKEL, M.D.
Boston, Massachusetts *Pittsburgh, Pennsylvania* *Cleveland, Ohio*

THE development of technics for the catheterization of the right side of the heart [*1*] and the coronary sinus [*2*] in man has made possible the study of the metabolism in the intact human heart. By observing the rate of coronary blood flow [*3*] and the coronary arteriovenous differences for the respiratory gases and such substrates as glucose, lactate and pyruvate, it has been possible to compute the rate of metabolic processes in the beating heart and to draw certain inferences about the sources of energy for myocardial contraction under both physiological and pathological conditions [*4*]. Differing patterns of myocardial metabolism have been observed previously in dogs in states of inanition [*5*], anoxia [*6*], athiaminosis [*7*] and hemorrhagic shock [*8–9*].

This report will present data pertaining to the myocardial metabolism in normal human subjects, fed and in the fasting state, and of patients with mild diabetes mellitus [*10*]. Early studies of the heart-lung preparation or of the isolated oxygenated heart by Starling [*11*], Evans [*12*] and Braun-Menendez [*13*] and their colleagues revealed that glucose, lactate and pyruvate were extracted from the coronary blood by such preparations. It was found, furthermore, that the metabolism in the isolated heart was altered by fasting and by diabetes mellitus. Cruikshank and McClure [*14*] reported that the fasting heart utilized only fat, and Evans et al. [*15*] concluded from studies of the oxygenated perfused diabetic dog heart that diabetes mellitus reduced the glucose uptake of cardiac muscle without influencing the lactate uptake. Cruikshank and Shrivastava [*16*] came to a similar conclusion. Although no data appeared to be available relative to the effect of diabetes mellitus upon pyruvate uptake of the perfused heart, Pearson et al. [*17*] reported a reduced extraction rate for pyruvate and a reduced conversion rate of pyruvate to carbon dioxide in slices of heart muscle from diabetic rats.

Studies of myocardial metabolism in intact dogs by catheterization of the coronary sinus [*5,18*] have shown that glucose, lactate and pyruvate are extracted by the normal heart *in vivo* in proportion to arterial concentration. These studies have also shown that fasting markedly reduces the extraction of carbohydrate and the cardiac respiratory quotient of the dog heart to a value near 0.70, consistent with a change from carbohydrate to fat oxidation. In this present study data are presented to demonstrate that the changes in cardiac metabolism in man with feeding and fasting are similar to those found in the dog and that the alterations in diabetes mellitus are similar to but not identical with those found in fasting. Preliminary reports of this research have been made [*10,19*].

MATERIALS AND METHODS

Data presented herein were obtained by cardiac catheterization in thirty-three human subjects. Full studies, including the measurement of coronary flow, myocardial extraction of oxygen, glucose, lactate and pyruvate, and myocardial respiratory quotient, were carried out on nine healthy control subjects and seven patients with mild diabetes mellitus. The seven mildly diabetic patients had little or no fasting glycosuria and no ketosis. Four were in the fasting state, three were studied postprandially. Only one was receiving insulin (20 units/day), and this had been withheld for forty-eight hours prior to the study. Of the nine control subjects, five were studied in the postprandial state, i.e., two to three hours after a light, low fat breakfast, and four were studied following an overnight fast. In

* From the Departments of Medicine and Biochemistry, Harvard Medical School; the Department of Nutrition, Harvard School of Public Health; the Medical Clinic, Peter Bent Brigham Hospital, Boston, Massachusetts; and the Department of Pathology, Western Reserve University School of Medicine at City Hospital, Cleveland, Ohio. Supported in part by grants-in-aid from the Life Insurance Medical Research Fund and the American Heart Association. A brief abstract of these findings appeared in the *Yale Journal of Biology & Medicine*, 28: 568, 1956.

† Established Investigator of the American Heart Association.

addition sixteen other patients were studied incidental to routine coronary catheterization to obtain evidence on myocardial oxygen extraction. Six of these were free of cardiomegaly and any metabolic abnormalities, two were anemic, and eight were polycythemic secondary to tetralogy of Fallot.

Premedication included the oral administration of phenobarbital (30 to 60 mg.) one to two hours before the procedure, followed by the intramuscular administration of Demerol® (50 to 100 mg.) to patients who showed apprehension or irritability at the time of venipuncture. Maintenance of a comfortable steady state throughout the procedure was possible under these conditions. All patients showed a normal pulse rate of 70 to 90 per minute and a normal mean arterial blood pressure of about 100 mm. Hg. Sampling procedures were the same as previously described [*1*] and analyses for oxygen, carbon dioxide, glucose, lactate and pyruvate were performed by methods already described [*3*].

DEFINITIONS

Myocardial extraction is the coronary arteriovenous difference of substrate (milligrams per cent) or gas (volumes per cent).

Myocardial extraction coefficient (A-V/A) is the myocardial extraction of a metabolite or gas (coronary arteriovenous difference) divided by the level of the same metabolite times 100. Under normal conditions the arteriovenous difference (A-V) of each metabolite is dependent upon the arterial level of that metabolite independent of other metabolites and independent of coronary blood flow. Changes in this index (A-V/A) are thus of some significance.

Myocardial utilization of a metabolite is the product of the coronary arteriovenous difference times coronary blood flow and is expressed as cubic centimeters of gas or milligrams of substrate per hundred grams of left ventricular myocardium per minute.

Myocardial respiratory quotient is the respiratory quotient for the myocardium and equals the myocardial carbon dioxide production divided by the myocardial oxygen consumption.

Myocardial carbohydrate oxidation coefficient is the percentage of total myocardial oxygen usage required for the oxidation of the carbohydrate (glucose plus lactate plus pyruvate) undergoing simultaneous extraction. This calculation assumes a steady state in cardiac metabolism, which is not always the case.

These parameters have been characterized in more detail in a previous paper [*3*].

RESULTS

Normal Man. In normal human subjects, a distinctive pattern of myocardial metabolism is noted in both the fasting and postprandial states. The major differences in substrate extraction are in consequence of different arterial levels in these two states. In the fasting state, the arterial levels of glucose, lactate and pyruvate are lower; consequently, the extraction of these substrates by the heart is lower. A direct dependence of myocardial extraction of each substrate upon its own arterial concentration regardless of the state of fasting or feeding in both man and normal anesthetized dogs [*3*] is shown in Figures 1, 2 and 3. No significant differences exist between the regression curves of the two species for any of the three carbohydrate substrates studied.

For each substrate there is a definite threshold of myocardial utilization. These are very low for lactate (2.5 ± 0.1 mg. per cent) and pyruvate (0.6 ± 0.2 mg. per cent). The threshold for glucose is considerably higher, no extraction occurring until the arterial level reaches 59 ± 6 mg. per cent. In the fasting state with blood sugar levels of 60 to 80 mg. per cent, a small coronary arteriovenous glucose difference exists which accounts generally for from 10 to 32 per cent of the simultaneous myocardial oxygen uptake. Following a light breakfast, the circulating glucose levels were somewhat higher, in the range of 80 to 124 mg. per cent, and higher coronary A-V glucose differences of 6 to 12 mg. per cent were found, accounting for from 50 to 80 per cent of the myocardial oxygen usage. The A-V/A for glucose, therefore, varies from 0 per cent at the threshold level to as much as 10 per cent at an arterial level of 100 mg. per cent.

The regression lines for lactate and pyruvate in the range studied seem to be perfectly linear. The regression line for the glucose extraction is curvilinear but not logarithmic as suggested by Bing [*9*]. There is no evidence to indicate that the limit on myocardial glucose extraction is 10 to 12 mg. per cent as suggested by Bing [*9*] but rather approaches 25 to 30 mg. per cent asymptotically at levels above 250 mg. per cent.

The myocardial respiratory quotient correlated well with the independently determined carbohydrate oxidation coefficient in the human subjects studied. Figure 4 presents the findings in man in the fasting state and fed compared with dogs in the fasting state and fed [*5*]. A linear relationship between myocardial respiratory quotient and the percentage of myocardial oxygen utilized for the oxidation of glucose, lactate and pyruvate was found, as would be expected if the extracted carbohydrate were quantitatively oxidized to carbon dioxide and

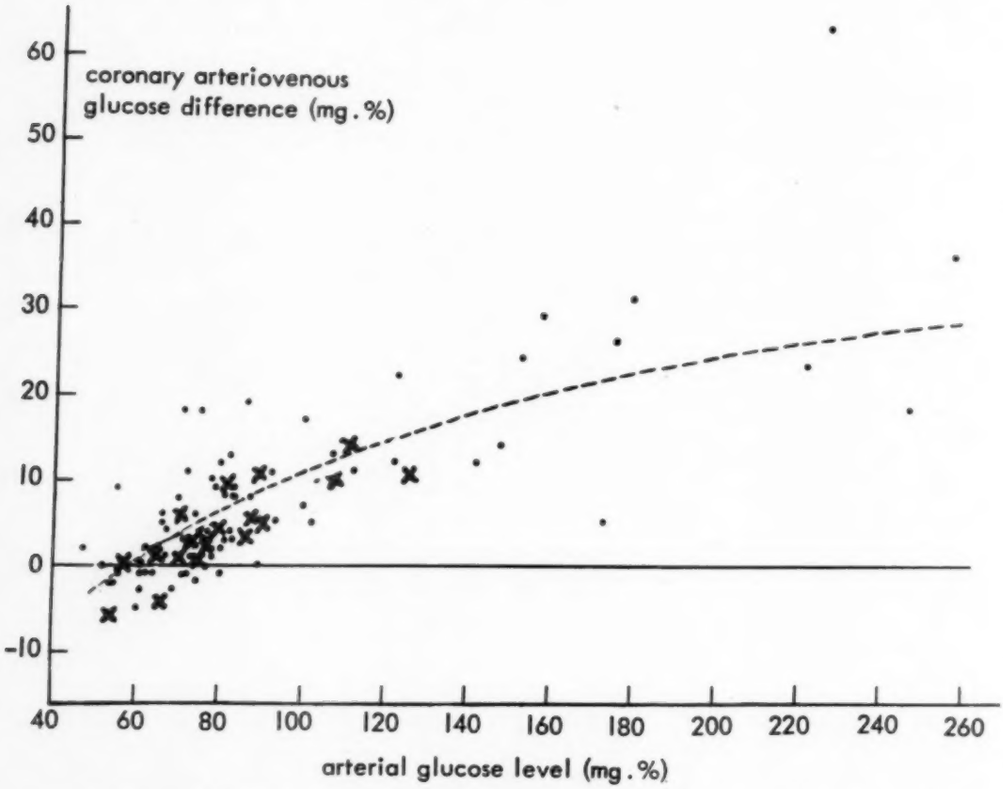


FIG. 1. Myocardial glucose extraction in relation to arterial glucose level; values in man (X) compared with those in dogs (dots).

water. During fasting in man and dogs carbohydrate extraction decreases, the respiratory quotient approaches 0.7 and the heart appears to subsist mainly on fat. Bing et al. [*20*], using a titrimetric method for *total* fatty acids, found that the human myocardium during fasting could derive up to 67 per cent of its energy from fatty acids. More recently, Gordon and Cherkes [*21*] have reported that the source of fatty acids for oxidation by heart, skeletal muscle and viscera is the non-esterified fatty acid fraction of the plasma which is albumin-bound. These workers measured this lipid fraction separately in arterial and coronary sinus blood samples from healthy subjects and found that from 25 to 70 per cent of the myocardial oxygen usage could be accounted for by combustion of the absorbed non-esterified fatty acids. The administration of glucose to their subjects lowered the non-esterified fatty acid concentration and abolished the uptake by the myocardium. Likewise, in our postprandial subjects carbohydrate extraction accounted for the bulk of the cardiac energy requirement. In fact, the extraction of total carbohydrate by the heart was slightly in excess of the theoretical requirement (estimated from respiratory quotient). It is likely that some (a relatively small fraction) of the absorbed glucose and 3-carbon acids is channeled into non-oxidative pathways yielding pentose (hexose-monophosphate shunt), glycerol plus intermediates of glycolysis, and amino acids. It appears that under normal conditions, however, [*20*] plasma amino acids provide only a small amount of oxidizable substrate for the heart.

The oxygen A-V/A or oxygen extraction ratio was remarkably constant in all twenty-six cases studied. Coronary arteriovenous differences were found to vary linearly with arterial oxygen level through a range from mild anemia to marked polycythemia as shown in Figure 5. The latter were observed in the patients with tetralogy of Fallot without cardiomegaly. It is remarkable that the A-V/A relationship applies so perfectly to oxygen extraction considering the fact that the source of "demand" for coronary arterial oxygen is the rate at which cytochrome oxidase is being reduced within the myocardial fibril.

It follows from this that the mechanism adjusting coronary flow must be extraordinarily sensitive to the needs of the hydrogen transport chain. Some "servo" mechanism must exist in order to "permit" the oxygen content of the arterial blood (ordinarily proportional to the hemoglobin concentration) to determine the myocardial oxygen extraction coefficient. It is, of course, well known that anoxia causes marked coronary vasodilation [*22*]. The equation for the regression line presented in Figure 5 is:

$$A_{O_2} - V_{O_2} = 0.65 \pm .06\ A_{O_2} + 0.13$$

The correlation coefficient for this regression is 0.98.

Diabetes Mellitus. In the diabetic patient myocardial glucose extraction is depressed, as has also been shown by Ungar et al. [*23*]. In the fasting human subject with mild diabetes the myocardial glucose extraction is negligible despite the presence of arterial glucose levels of 95 to 218 mg. per cent. (Table I.) The extraction of pyruvate and lactate by the diabetic heart at normal arterial levels of these substrates also is significantly decreased. In normal fasting patients the carbohydrate extraction oxidation index for glucose ranged from 13 to 31 per cent; in the diabetic fasting patients, it ranged from 0–6 per cent. Even the total carbohydrate extraction oxidation coefficient in the fasting diabetic heart was only 9 per cent (1 to 17 per cent) with a

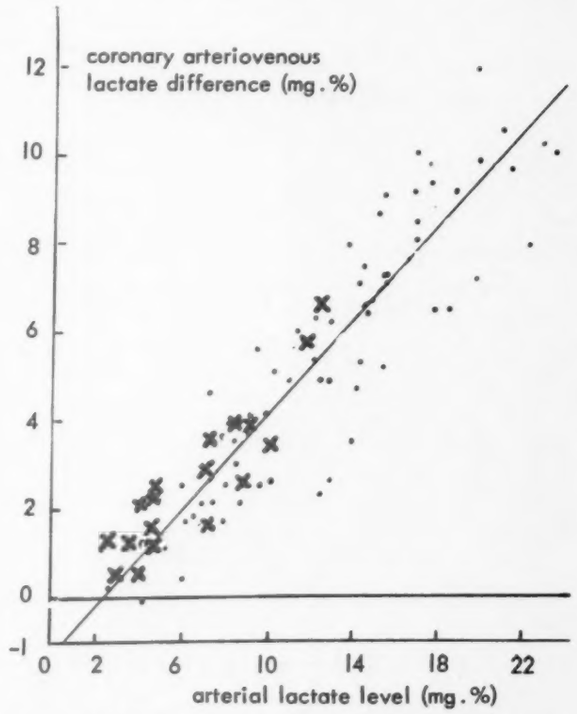


FIG. 2. Myocardial lactate extraction in relation to arterial lactate levels; values in man (X) compared with those in dogs (dots).

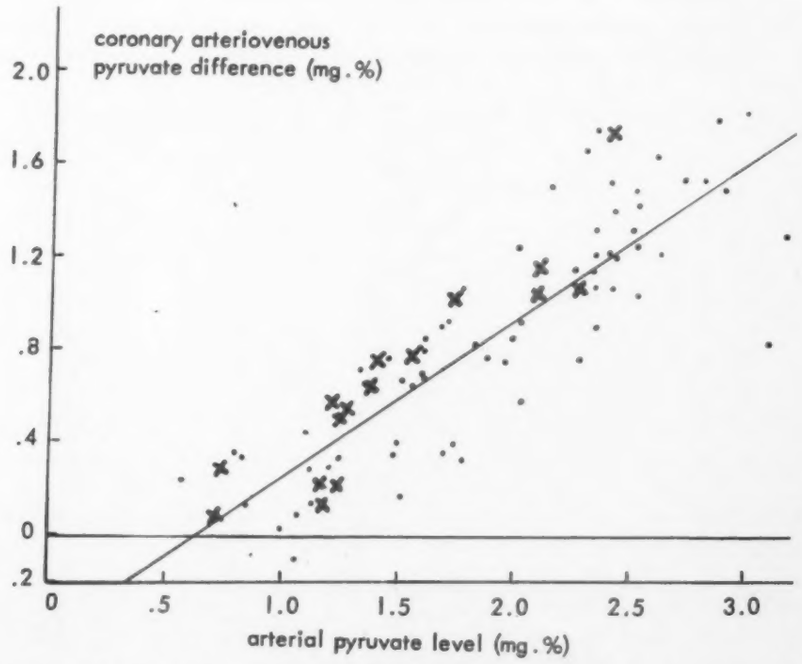


FIG. 3. Myocardial pyruvate extraction in relation to arterial pyruvate level; values in man (X) compared with those in dogs (dots).

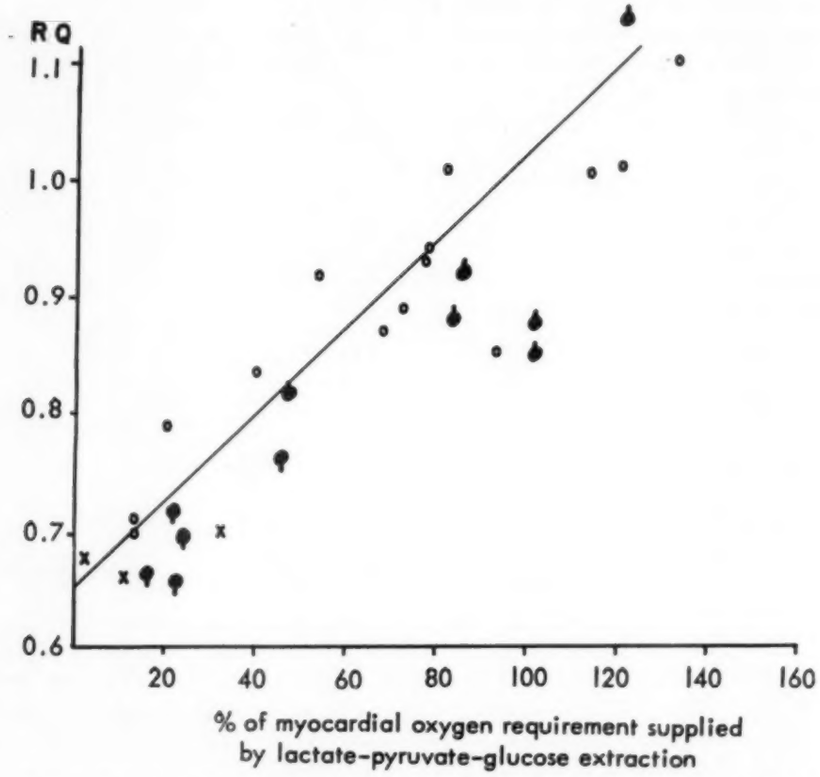


FIG. 4. Relation of myocardial R. Q. to myocardial carbohydrate extraction/oxidation ratio. Values in dogs are represented by open circles (normal series) and crosses (prolonged fasting); those in man by the solid circles with downward prongs (fasting) and solid circles with upward prongs (postprandial).

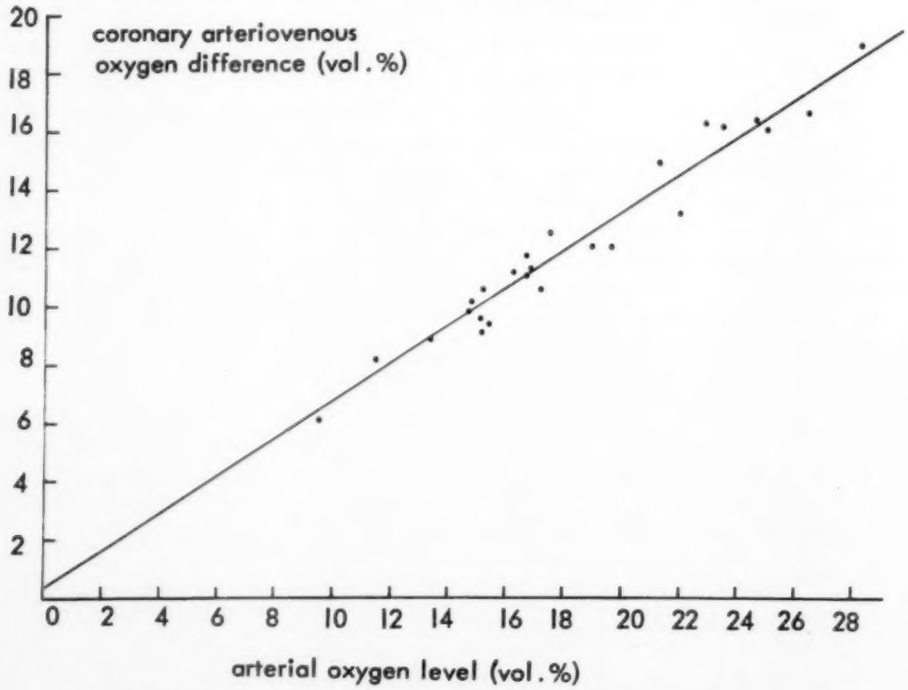


FIG. 5. Myocardial oxygen extraction in relation to arterial oxygen level in man.

TABLE I

METABOLIC FINDINGS IN NORMAL AND DIABETIC PATIENTS

Conditions	No.	Coronary Blood Flow (ml./100 gm./min.)	Oxygen (vol. %)			Glucose (mg. %)		Lactate (mg. %)		Pyruvate (mg. %)		Carbohydrate Oxidation Coefficient				R.Q.
			Arterial Saturation	Arterial	A-V	Arterial	A-V	Arterial	A-V	Arterial	A-V	Glucose (%)	Lactate (%)	Pyruvate (%)	Total (%)	
Normal Patients																
Fasting	1	99	98	14.8	9.8	80	4	5.2	1.5	.....	.....	31	11	..	42	0.77
	2	.....	....	14.7	10.1	72	2	4.0	0.4	.....	.....	15	3	..	18	0.67
	3	110	94	16.7	12.0	73	2	2.8	1.4	0.67	0.30	13	9	2	24	0.70
	4	.....	98	17.2	12.0	72	5	6.8	1.5	0.97	0.50	31	9	3	43	0.83
		(104)	(97)	(15.9)	(11.0)	(74)	(3)	(4.7)	(1.2)	(0.82)	(0.40)	(23)	(8)	(3)	(32)	(0.74)
Postprandial	1	97	98	15.1	10.8	91	10	5.1	2.1	1.40	0.72	69	15	4	88	0.89
	2	92	97	17.2	10.5	106	9	10.5	3.4	1.16	0.17	64	24	1	89	0.93
	3	.....	98	15.5	9.6	124	9	8.7	3.5	1.53	0.73	71	27	5	103	0.89
	4	95	95	16.7	11.1	110	12	6.8	2.7	1.24	0.44	81	18	3	102	0.85
	5	125	98	12.1	8.4	80	6	12.4	6.5	2.10	1.10	54	58	9	121	1.14
		(102)	(97)	(15.3)	(10.1)	(102)	(9)	(8.7)	(3.6)	(1.48)	(0.63)	(68)	(28)	(4)	(101)	(0.94)
Patients with Diabetes																
Fasting	1	.....	97	18.0	12.7	218	0	4.8	0.1	1.43	0.04	0	1	0	1	0.71
	2	.....	95	18.2	10.1	120	1	7.0	1.4	1.56	0.07	4	10	1	15	0.64
	3	80	88	16.3	12.9	95	1	7.3	1.7	1.64	0.21	6	10	1	17	0.71
	4	.....	95	16.8	12.0	130	0	6.5	0.8	1.60	0.19	0	5	1	6	0.73
		(80)	(94)	(17.3)	(11.9)	(141)	(1)	(6.4)	(1.0)	(1.56)	(0.13)	(5)	(7)	(1)	(10)	(0.70)
Postprandial	1	.....	96	16.2	9.2	267	9	8.0	2.5	1.91	0.42	73	20	3	96	0.80
	2	.....	99	17.1	11.6	185	23	10.1	2.9	2.08	0.40	148	19	2	169	0.65
	3	.....	....	18.0	11.9	171	13	9.8	2.1	2.06	0.31	82	13	2	97	0.66
		.....	(98)	(17.1)	(10.9)	(208)	(15)	(9.3)	(2.5)	(2.02)	(0.38)	(101)	(17)	(2)	(121)	(0.70)

NOTE: Figures in parentheses represent the mean.

TABLE II

EFFECTS OF CARBOHYDRATE INGESTION (100 GM.) AND INTRAVENOUS ADMINISTRATION OF CRYSTALLINE INSULIN (30 UNITS) IN DIABETES

	Oxygen (vol. %)		Glucose (mg. %)		Lactate (mg. %)		Pyruvate (mg. %)		Carbohydrate Oxidation Coefficient				R.Q.
	Arterial	A-V	Arterial	A-V	Arterial	A-V	Arterial	A-V	Glucose	Lactate	Pyruvate	Total	
Fasting	16.8	12.0	130	0	6.5	.8	1.60	.19	0	5	1	6	.73
1 hour postprandial	16.2	9.2	267	9	8.0	2.5	1.91	.42	76	21	3	100	.80
After insulin:													
20 min.	15.9	10.0	189	23	....	...	....	....	...	..	..	...	.93
25 min.	15.7	9.8	179	29	8.9	3.1	1.93	.76	210	24	5	239	1.17
35 min.	....	....	127	24	....	...	....	....	...	..	..	...	....
40 min.	16.3	10.3	102	6	9.0	4.1	1.91	.82	44	30	5	79	.92
50 min.	....	....	70	4	....	...	....	....	....	..	..	...	....
60 min.	16.5	12.1	67	4	13.1	6.1	2.33	1.00	25	38	6	69	.90

myocardial respiratory quotient of 0.64 to 0.73. This is consistent with the view that the heart in subjects with diabetes burns fat almost exclusively.

Ungar et al. [*23*] have observed that the diabetic human heart utilizes more fatty acids than does the non-diabetic heart, and Dole [*24*] has noted that the non-esterified fatty acid fraction of the serum lipids is greatly elevated in diabetes in man.

Diabetic patients showed a rise in myocardial extraction of glucose, lactate and pyruvate postprandially but this occurred at an appreciable elevation of the arterial concentrations of these

metabolites, so that the myocardial extraction coefficients for all three substances were still depressed below normal.

The effects of administration of glucose and insulin upon myocardial metabolism in diabetes are shown in Table II. The administration of glucose alone to a fasting diabetic patient increased the myocardial extraction of glucose, lactate and pyruvate but raised the myocardial respiratory quotient only from 0.73 to 0.80. Although the total carbohydrate oxidation coefficient rose from 6 to 100 per cent, the relatively small effect upon respiratory quotient indicated that only a small fraction of the extracted carbohydrate was being oxidized. With the administration of insulin, however, there was an even more pronounced rise in myocardial extraction coefficients for glucose, pyruvate and lactate to normal, a rise in myocardial respiratory quotient to 1.17, and a marked hyperextraction of total carbohydrate to account for a hypothetical 239 per cent of the simultaneously observed oxygen extraction. It would thus appear that insulin promotes the non-oxidative as well as oxidative utilization of carbohydrate by the heart.

DISCUSSION

The similarity of myocardial extraction coefficients in man to those in anesthetized dogs helps to establish these A-V/A values as significant characteristics of the normal myocardium. Various abnormal metabolic states such as athiaminosis [*5*], starvation [*3*], anoxia [*4*] and hemorrhagic shock [*6*] in dogs are characterized by abnormal myocardial extraction coefficients for glucose, pyruvate, lactate and oxygen.

A short period of fasting *per se* in the normal human subject does not influence the myocardial extraction coefficient, coronary arteriovenous differences being lowered by virtue of lowered arterial levels of extractable carbohydrate. Patients with mild diabetes, on the other hand, show distinctly reduced myocardial extraction coefficients, particularly for glucose but also for lactate and pyruvate in both the fasting and postprandial conditions. Insulin appears to influence glucose metabolism at an early stage. Levine et al. [*25*] have adduced evidence to suggest that cellular permeability to glucose in muscle and adipose tissue is under the control of insulin. In our diabetic patient the administration of insulin resulted in restoration of a normal myocardial glucose extraction coefficient and stimulation of carbohydrate oxidation by the heart, consistent with this hypothesis.

Arterial glucose is normally treated as a high threshold substance by the myocardium, very little extraction occurring below 59 ± 6 mg. per cent. In diabetes mellitus this threshold is further elevated. Although diabetic subjects in the postprandial state extracted more glucose than those in the fasting condition, the myocardial extraction coefficient was markedly reduced. Only with insulin treatment did a normal relationship between arterial level and extraction return, i.e., 29 mg. per cent extracted at an arterial level of 179 mg. per cent.

The administration of large doses of insulin to normal dogs has been found to lower the threshold for myocardial utilization of glucose from 59 ± 5 mg. per cent to 10 ± 3 mg. per cent [*26*]. It seems reasonable, therefore, to conclude that the threshold for glucose utilization by the myocardium is under hormonal control. It is of some interest that slices of cardiac muscle *in vitro* do not manifest this threshold behavior, metabolizing added glucose at very low concentrations [*27*].

The diabetic patient also shows a reduced ability to extract pyruvate and lactate from arterial blood, a defect not entirely consistent with a single action of insulin on cell permeability. The reduced myocardial extraction coefficients for lactate and pyruvate were restored to normal by insulin therapy. These results are consistent with some whole animal and surviving tissue experiments in which it has been found that the metabolism of acetate and pyruvate are disturbed in the diabetic organism. Charlampous and Hegsted [*28*] found that acetylation of paraaminobenzoic acid was decreased in alloxan-diabetic rats, and Frohman and Orten [*29*] have postulated a block in acetate metabolism at the level of the Krebs cycle in such animals. Guggenheim and Olson [*30*] have reported decreased oxidation rates of acetate-1-C^{14} and pyruvate-2-C^{14} in intact alloxan-diabetic rats, although more recent experiments in our laboratory show that this depression is due to over-all reduced carbon dioxide production in these rats. Pearson et al. [*17*], furthermore, have reported decreased rates of pyruvate oxidation by diabetic rat diaphragm which are restored towards normal by the administration of insulin. Vester and Stadie noted decreased pyruvate utilization and decreased oxidative phosphorylation in liver mitochondria from diabetic cats [*31*]. On the

other hand, Flock and Bollman [*32*] found that pyruvate given intravenously was utilized normally in diabetic dogs. The precise change in the diabetic human heart responsible for decreased pyruvate extraction is not evident. It is reversed by the administration of insulin. Further research is necessary before the controversial experimental data on pyruvate metabolism in diabetes are clarified.

The coronary A-V/A for oxygen is surprisingly constant in the patients examined during this study despite wide variations in hemodynamics such as are encountered in cases of marked secondary polycythemia and anemia. Case, Berglund and Sarnoff [*33*] have recently confirmed the constancy of the myocardial coefficient for oxygen extraction over a wide range of conditions including variations in left ventricular work, left atrial filling pressure, coronary blood flow and hematocrit. In mild diabetes no abnormality in oxygen A-V/A was found, although in severe diabetic acidosis a reduced coefficient such as that seen in athiaminosis [*7*] would certainly not be unexpected.

The subjects with mild diabetes studied showed no hemodynamic signs of cardiac failure of metabolic origin. In all cases, heart size, vital capacity, circulation time and response to exercise were normal. Thus in diabetes of this severity there appeared to be no threat to cardiac competence. The diabetic heart probably adapts itself to this biochemical lesion in carbohydrate metabolism by a greater dependence upon fat as a source of energy.

SUMMARY

1. The normal human heart extracts glucose. lactate, pyruvate and oxygen in direct relation to the arterial blood level of each metabolite, independent of other factors. This phenomenon, which is shared with the dog, is best expressed by computing the myocardial extraction coefficient (A-V/A) for each metabolite.

2. Fasting in normal human subjects is accompanied by a decline in arterial blood levels of glucose, pyruvate, and lactate, and by a decreased myocardial extraction of carbohydrate substrate. The myocardial respiratory quotient averages 0.74, suggesting a major dependence upon fat for energy production.

3. In the postprandial state human subjects extract enough total carbohydrate to account for the entire oxygen consumption of the heart. The myocardial respiratory quotient is 0.90, which suggests, however, that some of the energy production of the heart is accounted for by fat under these conditions and that some of the extracted carbohydrate is used for non-oxidative purposes.

4. In fasting subjects with mild diabetes the myocardial glucose extraction was nil and the extraction of lactate and pyruvate markedly reduced despite increased arterial blood levels of glucose and normal levels of lactate and pyruvate. The myocardial respiratory quotient averaged 0.70, consistent with exclusive fat oxidation.

5. Administration of glucose or a meal to diabetic subjects resulted in markedly increased arterial blood glucose levels and some increase in myocardial extraction. Only simultaneous administration of insulin restored the myocardial extraction coefficients for glucose, pyruvate and lactate to normal.

REFERENCES

1. Sosman, M. C. and Dexter, L. Venous catheterization of the heart. *Radiology*, 48: 441, 1947.
2. Bing, R. J., Vandam, L. D., Gregoire, F., Handelsman, J. C., Goodale, W. T. and Eckenhoff, J. E. Catheterization of the coronary sinus and middle cardiac vein in man. *Proc. Soc. Exper. Biol. & Med.*, 66: 239, 1947.
3. Goodale, W. T. and Hackel, D. B. Measurement of coronary blood flow in dogs and man from rate of myocardial nitrous oxide desaturation. *Circulation Res.*, 1: 502, 1953.
4. Olson, R. E. and Schwartz, W. B. Myocardial metabolism in congestive heart failure. *Medicine*, 30: 21, 1951.
5. Goodale, W. T. and Hackel, D. B. Myocardial carbohydrate metabolism in normal dogs with effects of hyperglycemia and starvation. *Circulation Res.*, 1: 509, 1953.
6. Hackel, D. B., Goodale, W. T. and Kleinerman, J. Effects of hypoxia on the myocardial metabolism of intact dogs. *Circulation Res.*, 2: 169, 1954.
7. Hackel, D. B., Goodale, W. T. and Kleinerman, J. Effects of thiamine deficiency on myocardial metabolism in intact dogs. *Am. Heart J.*, 46: 1, 1953.
8. Hackel, D. B. and Goodale, W. T. Effects of hemorrhagic shock on the heart and circulation of intact dogs. *Circulation Res.*, 11: 628, 1955.
9. Bing, R. J., Siegal, A., Vitale, A., Balboni, F., Sparks, E., Taeschler, M., Klapper, M. and Edwards, S. Metabolic studies on the human heart *in vivo*. I. Studies on carbohydrate metabolism of the human heart. *Am. J. Med.*, 15: 284, 1953.
10. Goodale, W. T., Olson, R. E. and Hackel, D. B. Contrasting patterns of myocardial metabolism in diabetes, cardiac failure, and after insulin administration in man. In: Nineteenth International Physiological Congress, Montreal, 1953.

11. Patterson, S. W. and Starling, E. H. The carbohydrate metabolism of the isolated heart-lung preparation. *J. Physiol.*, 47: 137, 1913–1914.
12. Evans, C. L. Metabolism of the heart. *Edinburgh M. J.*, 46: 733, 1939.
13. Braun-Menendez, E., Chute, A. D. and Gregory, R. A. Usage of pyruvic acid by the dog's heart. *Quart. J. Physiol.*, 21: 91, 1939.
14. Cruikshank, E. W. H. and McClure, G. S. On the question of utilization of amino acids and fat by mammalian heart. *J. Physiol.*, 86: 1, 1936.
15. Evans, C. L., Grande, F., Hsu, F. Y., Lee, D. H. K. and Mulder, A. C. Glucose and lactate usages of diabetic heart and influence of insulin thereon. *Quart. J. Physiol.*, 24: 365, 1935.
16. Cruikshank, E. W. H. and Shrivastava, D. L. Action of insulin on storage and utilization of sugar by isolated normal and diabetic heart. *Am. J. Physiol.*, 92: 144, 1930.
17. Pearson, O. H., Hsieh, C. K., Dutoit, C. H. and Hastings, A. B. Metabolism of cardiac muscle: utilization of C^{14}-labeled pyruvate and acetate in diabetic rat heart and diaphragm. *Am. J. Physiol.*, 158: 261, 1949.
18. Goodale, W. T., Lubin, M., Eckenhoff, J. E., Hafkenschiel, J. H. and Banfield, W. G. Coronary sinus catheterization for studying coronary blood flow and myocardial metabolism. *Am. J. Physiol.*, 152: 350, 1948.
19. Goodale, W. T., Olson, R. E. and Hackel, D. B. The effect of mild diabetes and insulin on heart muscle metabolism in man. *J. Clin. Invest.*, 30: 642, 1951.
20. Bing, R. J., Siegal, A., Ungar, I. and Gilbert, M. Metabolism of the human heart. II. Studies on fat, ketone and amino acid metabolism. *Am. J. Med.*, 16: 504, 1954.
21. Gordon, R. S. and Cherkes, A. Unesterified fatty acid in human blood plasma. *J. Clin. Invest.*, 35: 206, 1956.
22. Eckenhoff, J. E. and Hafkenschiel, J. H. The oxygen content of coronary venous blood as affected by anoxia and cytochrome C. *Am. Heart J.*, 36: 3, 1948.
23. Ungar, I., Gilbert, M., Siegal, A., Blair, J. M. and Bing, R. J. Studies on myocardial metabolism. *Am. J. Med.*, 18: 385, 1955.
24. Dole, V. P. Transport of non-esterified fatty acids. In: Chemistry of Lipides as Related to Atherosclerosis, p. 189. Springfield, Ill., 1958. Charles C Thomas.
25. Levine, R. and Goldstein, M. S. On Mechanism of Action of Insulin Recent Progress in Hormone Research, vol. 11, p. 343. Edited by Pincus, G. New York, 1955. Academic Press Inc.
26. Hackel, D. B. Private communication.
27. Olson, R. E. and Piatnek, D. A. Conservation of energy in cardiac muscle. *Ann. New York Acad. Sc.*, 72: 466, 1959.
28. Charlampous, F. C. and Hegsted, D. M. Acetylation in the diabetic rat. *J. Biol. Chem.*, 180: 623, 1949.
29. Frohman, C. E. and Orten, J. M. Tracer studies of acids of the tricarboxylic acid cycle. II. Effect of fructose and bicarbonate on acetate metabolism in livers of diabetic rats. *J. Biol. Chem.*, 220: 315, 1956.
30. Guggenheim, K. and Olson, R. E. The oxidation of radioactive pyruvate and acetate in pantothenic acid and thiamine deficient and in diabetic rats. *Acta med. orient.*, 12: 255, 1953.
31. Vester, J. W. and Stadie, W. C. Studies of oxidative phosphorylation by hepatic mitochondria in the diabetic cat. *J. Biol. Chem.*, 227: 669, 1957.
32. Flock, E. V. and Bollman, J. L. and Mann, F. C. The utilization of pyruvic acid by the dog. *J. Biol. Chem.*, 125: 49, 1938.
33. Case, R. B., Berglund, E. and Sarnoff, S. J. Ventricular Function. VII. Changes in coronary resistance and ventricular function resulting from acutely induced anemia and the effect thereon of coronary stenosis. *Am. J. Med.*, 18: 397, 1955.

Proteins, Lipoproteins and Protein-Bound Carbohydrates in the Serums of Diabetic Patients*

PEDRO EJARQUE, M.D., ALEXANDER MARBLE, M.D. *and* ELIZABETH F. TULLER, PH.D.

Chicago, Illinois *Boston, Massachusetts* *Kalamazoo, Michigan*

In recent years there has been an increasing awareness of the problems posed by changes in the vascular system which occur concomitantly with the increased life span of the diabetic person [*1*]. The disabling effects of these vascular changes and the increasing mortality due to nephropathy in younger diabetic persons and to coronary artery disease in older persons with diabetes have focused attention on the cause of these conditions.

Since histochemical examination of certain vascular lesions reveals the presence of both mucopolysaccharide and lipid materials in high concentrations [*2,3*], a number of studies of the serum protein fractions and their conjugates have been made in an attempt to determine the mechanism of production and the metabolic changes involved in these vascular alterations. These investigations have included chemical determination of the protein-bound carbohydrates [*4–11*], ultracentrifugal studies of the serum lipoproteins [*12–14*] and paper or zone electrophoretic studies of the serum proteins and their conjugates [*15–25*]. The results have shown that not only may abnormal values be found for certain of the serum proteins and their conjugates in the presence of retinopathy and nephropathy, but also that changes are present in the serums of diabetic persons before there is overt clinical evidence of the vascular complications [*15–21*].

The number of patients with diabetes seen in the New England Deaconess Hospital and in the Joslin Clinic affords a unique opportunity to study young persons with onset of the disease prior to the age of thirty years and in whom changes due to the aging process are minimized and effects due to diabetes accentuated. Consequently, it was thought worthwhile to carry out a study in which there would be an opportunity to correlate the degree of control of diabetes and age at onset and duration of diabetes with changes in the serum proteins as determined by paper electrophoresis. Furthermore, it was thought desirable to use a single basic technique which would permit the simultaneous study of the serum proteins and their conjugates by separation of the principal serum protein fractions with paper electrophoresis followed by appropriate stains for the determination of the protein moiety, the lipoproteins and the protein-bound carbohydrates. When completed the study included sixty-four diabetic patients and fourteen non-diabetic persons.

METHODS

The fourteen non-diabetic persons were physicians and technicians in apparent good health and ranged in age from twenty to fifty years. The sixty-four diabetic patients were from fifteen to fifty-five years of age and all but nine were inpatients at the New England Deaconess Hospital. Nine were outpatients from the Joslin Clinic. Except for age, the only criterion for selection of these patients was the absence of all active infection, hepatic disease, acidosis, and other conditions, aside from diabetes itself, which are known to affect the serum proteins and their conjugates.

All blood samples were taken either following an overnight fast or no sooner than three hours after eating. The blood was allowed to stand at 4°C. for a minimum of forty-five minutes and the serum was separated in a refrigerated centrifuge at 2,000 R.P.M. for thirty minutes. Hematocrit and total protein

* From the Baker Clinic Research Laboratory, New England Deaconess Hospital and the Joslin Clinic, Boston, Massachusetts. This investigation was supported in part by grants from the Diabetic Fund of Boston and the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Public Health Service Grants A-525-A-525 (C2).

TABLE 1
CLINICAL DATA FOR DIABETIC SUBJECTS

Case No.	Sex	Age (yr.)	Age at Onset (yr.)	Duration of Diabetes (yr.)	Diet			Daily Insulin Dose (units)	Control*
					Carbohydrates (gm.)	Protein (gm.)	Fat (gm.)		
Diabetic Subjects without Complications (D_1)									
5	M	24	11	13	186	125	125	72	P
6	F	24	8	16	200	68	77	42	P
7	F	55	29	26	174	66	55	44	G
9	M	37	27	10	181	100	100	80	G
12	M	49	49	0	20	250	150	150	UC
13	M	58	34	24	159	93	92	40	F
15	M	34	29	5	181	93	98	48	F
16	F	19	11	8	64	151	78	81	P
18	F	41	28	13	151	72	78	40	F
22	M	27	20	7	176	75	28	48	UC
24	F	21	16	5	180	80	20	80	P
26	M	43	43	0	151	78	81	0	N
28	M	22	5	17	150	70	70	34	P
29	F	43	43	0	140	70	69	64	UC
30	M	41	41	0	149	76	73	18	UC
31	F	54	54	0	162	76	70	0	UC
32	F	25	20	5	100	51	65	60	F
35	F	16	15	1	151	83	79	38	UC
36	M	56	54	2	172	97	73	8	UC
40	F	54	45	9	150	70	70	14	P
41	M	23	12	11	197	93	50	72	G
42	M	55	53	2	181	93	102	38	F
45	F	54	26	29	189	121	172	64	G
Diabetic Subjects with Neuropathy (D_2)									
3	M	43	32	11	169	84	102	32	F
20	F	29	26	3	139	69	60	48	F
21	M	38	35	3	151	64	71	56	F
23	F	52	41	11	169	81	77	40	F
27	F	54	30	24	118	55	49	17	G
39	F	55	31	24	163	78	77	48	UC
43	M	53	46	7	169	98	111	48	P
48	F	52	42	10	158	63	77	40	P
50	M	52	40	12	177	80	75	6	G
Diabetic Subjects with Retinopathy (D_3)									
8	F	20	11	9	122	56	44	68	G
10	F	52	28	24	163	78	79	34	P
11	M	39	21	18	184	93	79	40	P
14	M	29	11	18	167	73	80	40	F
17	M	27	9	18	161	104	111	104	P
19	M	33	12	21	169	88	90	74	P
25	M	33	5	28	180	90	85	60	P
47	F	22	4	18	151	64	75	45	P
53	F	51	26	25	126	57	39	64	P
54	M	40	23	17	178	107	125	58	G
56	M	56	52	4	154	83	56	8	G
60	M	45	27	18	151	80	88	44	P
63	F	56	46	10	148	68	62	20	P

TABLE 1 (*Continued*)

CLINICAL DATA FOR DIABETIC SUBJECTS

Case No.	Sex	Age (yr.)	Age at Onset (yr.)	Duration of Diabetes (yr.)	Diet			Daily Insulin Dose (units)	Control*
					Carbohydrate (gm.)	Protein (gm.)	Fat (gm.)		
Diabetic Subjects with Retinopathy and Neuropathy (D_4)									
33	M	38	22	16	179	91	89	84	P
34	F	51	44	7	160	75	80	40	P
44	M	40	27	13	211	118	122	54	G
51	M	53	32	21	163	90	81	52	F
52	M	57	51	6	180	81	75	40	F
55	F	41	19	22	...	...	...	25	F
58	F	53	28	25	192	72	53	12	G
64	M	27	8	19	...	...	...	50	P
65	F	64	45	19	...	...	...	40	P
Diabetic Subjects with Retinopathy, Nephropathy and Neuropathy (D_5)									
1	M	41	25	26	169	77	89	36	P
2	M	34	14	20	149	63	58	56	P
38	M	38	28	10	181	92	108	56	P
46	M	42	28	14	159	90	92	34	P
49	F	33	15	18	147	74	39	42	P
61	F	51	38	13	133	58	59	12	F
62	F	36	9	27	163	67	70	36	F
66	M	35	16	19	165	93	100	76	P
Diabetic Subjects with Retinopathy and Nephropathy (D_6)									
4	M	35	6	29	160	80	80	64	F
57	M	53	26	27	121	80	90	100	P

* Control of diabetes: G = good; F = fair; P = poor; UC = unclassified.

determinations were made; in the latter, a modification of the biuret method of Mehl [*26*] was followed.

Paper electrophoresis was carried out in the cold room (4°C.) by a modified technique of Grassmann and Hannig [*27*]. Whatman No. 1 paper was used with a veronal-acetate buffer (pH 8.60 to 8.65) for seventeen hours at 150 volts and 7 ma. The serum was applied in a 1 or 2 cm. band in different amounts corresponding to the analyses to be made, i.e., 0.005 ml. for proteins, 0.02 ml. for lipids, and 0.04 ml. for the protein-bound carbohydrates. A brief description of the technique used for each of these analyses follows:

The strips to be analyzed for the protein moieties were dried in the open air at room temperature for at least six hours. The strips were then stained for ten minutes in a solution of Amido black 10B (100 mg. in 100 ml. of 9:1 methyl alcohol-glacial acetic acid solution). The excess dye was removed in a series of phenol-glacial acetic acid wash solutions and the strips then dried overnight at room temperature. The strips were made translucent (α-bromonaphthalene-mineral oil mixture, $\mu = 1.51$) and read in a photovolt No. 525 densitometer at 600 mμ. The resultant curves were divided into the principal serum protein fractions and the corresponding areas determined with a planimeter.

The lipoproteins were determined by staining the lipids with Sudan Black B using an early modification of Peterson's method [*28,29*]. The wet strips were placed in a drying oven at 90° to 95°C. for twenty minutes and then stained for two hours at 40°C. in a saturated solution of the dye (100 mg. in 100 ml. of 30 per cent methyl alcohol, 30 per cent isopropyl alcohol, and 40 per cent water). The excess dye was then removed by washing the strips in 30 per cent isopropyl alcohol for five minutes in each of six baths and air-dried in the dark on glass plates. The densities and areas of the curves were determined in the same manner as for the proteins.

The protein-bound carbohydrates were stained by a modification of the periodic acid-Schiff procedure of

Köiw et al. [*30*]. The strips were dried at 90° to 95°C. for twenty minutes, placed in absolute alcohol and then in the periodic acid bath. After ten minutes the strips were washed in 70 per cent ethyl alcohol, transferred to the reducing solution until barely yellow, and finally into a fuchsin-sulfite solution for thirty minutes. The excess fuchsin was removed by ten successive five-minute washes in sulfite rinse water. The backgrounds were entirely discolored. The strips were then dried in a stream of air. The strips were not washed with water or dehydrated with ethanol before drying since it was found that either of these steps caused an increase of albumin and γ-globulin not proportional to the increase of the other globulin fractions. Densities were determined using a green filter (530 mμ.) and the areas for each fraction found with the aid of a planimeter.

RESULTS

The data obtained in this investigation are presented in three sections, i.e., proteins, lipoproteins (stainable lipids) and protein-bound carbohydrates. Data for all three components were obtained for the fourteen non-diabetic and the sixty-four diabetic persons. The latter have been subdivided into groups based on clinical diagnosis and these groups have been designated as follows: D-1, without vascular complications; D-2, with neuropathy only; D-3, with retinopathy only; D-4, with retinopathy and neuropathy; D-5, with retinopathy, neuropathy and nephropathy ("triopathy"); and D-6, with retinopathy and nephropathy. All groups of diabetic patients consisted of eight or more persons except the last, which consisted of only two. Since in every type of determination the results in this group (D-6) fell within the range of the triopathy cases, and since in a previous study [*23*] results in the two groups (D-5 and D-6) had been shown to be statistically comparable, they were combined as D-5,6.

Retinopathy, nephropathy and neuropathy were diagnosed on the basis of general criteria used by the Joslin Clinic [*31*].

In Table I are given the clinical data regarding the patients with diabetes.

Principal Serum Protein Fractions. Table II presents the mean values obtained for each of the principal serum protein fractions. The data are given both in relative (per cent of total planimeter area) and absolute (grams per cent) percentages. Since in a majority of reports in the literature only relative percentages are given, these are included in Table II for comparative purposes. However, the subsequent discussion is based primarily on the changes in the grams per cent or absolute amount of the protein fractions.

As might be expected there is a significant decrease in the amount of albumin in the serum with the appearance of renal damage (group D-5,6). However, there is also a sharp and statistically significant* drop in the amount of serum albumin even in diabetic persons without any clinically recognizable vascular complications.

The α_1- and β-globulin fractions showed no significant change in any diabetic group.

Although it is evident from an examination of the data presented in Table II that there is an increase in the α_2-globulin fraction in the serums of diabetic persons without complications (D-1) as well as in those with triopathy (D-5,6), the scatter is sufficiently large in these small groups so that the differences only border on significance ($p \leqq 0.05$).

In general, the values for the γ-globulin fraction are significantly low only in the presence of retinopathy and nephropathy (D-5,6). Interestingly enough, although the scatter is quite large, the diabetic persons with retinopathy only (D-3) show a definite decrease from normal ($0.05 > p < 0.01$).

Lipoproteins. The technique used in staining the lipids made possible only qualitative results. Furthermore, since in the final analysis only two major components are dealt with and since one of them is an extremely large fraction of the total lipoprotein measured, relative percentages may not always give an accurate picture of the relationships found. Therefore, the areas measured with the planimeter were used in determining possible changes. Table III shows the data given both ways. Since the scatter was large and some of the groups small, a scattergram of the areas found for the α- and β-lipoproteins in the serums of both non-diabetic and diabetic persons is given in Figure 1. It is evident that in the group of diabetic patients with complications (D-2, D-3, D-4, D-5,6), 74 per cent of the values of the β-lipoproteins are above the normal mean, while the values for diabetic persons without complications follow a more nearly normal distribution. The over-all range of the areas determined for the α-lipoprotein fraction appears to be about the same for the normal and for the diabetic person. This is particularly true in the diabetic patients

* Whenever the term "statistically significant" is used, the T test has indicated that $p \leqq 0.01$.

TABLE II
VALUES FOR THE SERUM PROTEINS AND THEIR FRACTIONS

Patients		Total Protein		Albumin		Globulins							
						α_1		α_2		β		γ	
No.	Groups	%	S.D.	%	S.D.	%	S.D.	%	S.D.	%	S.D.	%	S.D.
Protein Fractions—Per cent of Total Protein													
14	N	...	.....	57.8	±3.13	4.3	±0.80	8.4	±1.48	12.4	±1.22	16.9	±2.77
23	D_1	...	.....	51.7	±4.47	5.4	±1.20	10.8	±2.65	13.8	±1.26	17.9	±2.75
9	D_2	...	.....	55.1	±4.53	5.8	±1.70	10.1	±2.36	13.1	±1.26	15.5	±2.73
13	D_3	...	.....	52.9	±6.18	5.3	±0.94	11.9	±3.52	14.2	±1.98	15.8	±3.38
9	D_4	...	.....	56.6	±3.15	5.0	±0.76	9.9	±1.51	12.9	±1.30	15.5	±1.18
10	$D_{5,6}$	...	.....	52.4	±2.33	5.4	±3.15	12.7	±2.22	14.5	±2.66	14.9	±2.96
Proteins (gm. %)													
14	N	7.4	±0.38	4.3	±0.49	0.31	±0.06	0.61	±0.11	0.90	±0.08	1.24	±0.23
23	D_1	7.0	±0.80	3.6	±0.49	0.37	±0.08	0.75	±0.20	0.96	±0.19	1.19	±0.20
9	D_2	6.7	±0.81	3.7	±0.66	0.38	±0.10	0.66	±0.13	0.89	±0.10	1.05	±0.30
13	D_3	6.2	±1.37	3.2	±0.64	0.32	±0.09	0.75	±0.29	0.87	±0.23	0.98	±0.35
9	D_4	6.8	±0.73	3.9	±0.39	0.34	±0.12	0.67	±0.12	0.88	±0.16	1.09	±0.19
10	$D_{5,6}$	6.1	±0.15	3.2	±0.62	0.34	±0.08	0.79	±0.23	0.90	±0.26	0.91	±0.21

NOTE: N = Healthy, non-diabetic subjects.
D_1 = Diabetic without complications.
D_2 = With neuropathy only.
D_3 = With retinopathy alone.
D_4 = With retinopathy and neuropathy.
D_5 = With retinopathy, neuropathy and nephropathy.
D_6 = With retinopathy and nephropathy.

without complications. However, the diabetic patients with advanced vascular complications (D-5,6) show a majority of values (eight) distinctly below the normal mean.

Protein-bound Carbohydrate. The means of the total planimeter areas representing the total amount of protein-bound carbohydrate in each of the groups are given in Table IV. Also given are the relative percentages for each protein-bound carbohydrate fraction. The total amount of carbohydrate measured by this method is about equal to or somewhat increased over the normal values in each diabetic group except that of diabetic subjects with complications (D-1). In this group the values fell below the normal levels of total carbohydrate-staining material. The relative amount of the protein-bound carbohydrate in the α_2-globulin fraction is increased significantly in each diabetic group over that for the normal group. Standard deviations are given for α_2-globulin fraction only since this is the one fraction showing significant change.

TABLE III
SERUM LIPOPROTEIN FRACTIONS OF NON-DIABETIC AND DIABETIC PERSONS

Patients		Areas (mean—sq. cm.)		Per cent of Total (mean)	
No.	Groups	β	α	α	β
14	N	7.9	2.6	75.5	25.2
23	D_1*	8.2	2.3	78.2	21.6
9	D_2	7.6	2.6	74.8	26.0
13	D_3	10.0	2.4	80.2	19.3
9	D_4	8.3	2.1	78.5	20.8
10	$D_{5,6}$	9.3	1.9	82.1	17.1

* The designation of diabetic groups is explained in the footnote of Table II.

COMMENTS

The changes found in the values for the principal serum protein fractions are in the albumin, α_2-globulin and γ-globulin moieties. The decrease in the albumin and the increase in the

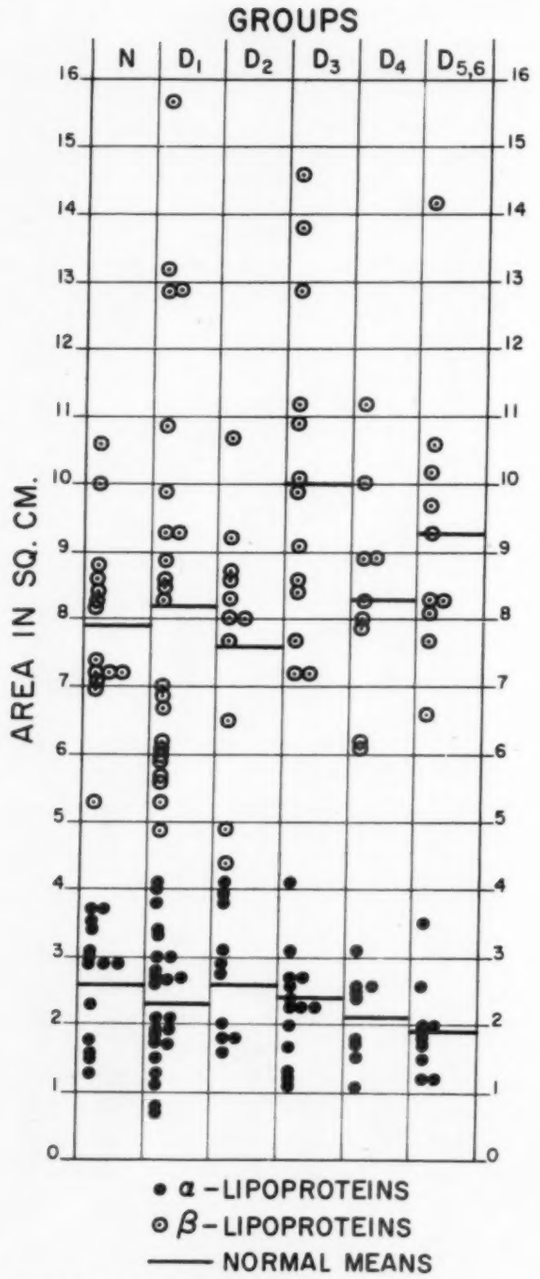


FIG. 1. Distribution of lipoprotein fractions in the serums of non-diabetic and diabetic subjects.

α_2-globulin components confirm work performed in this laboratory and elsewhere [*15–19,21,22*]. The decrease in the amount of the γ-globulin fraction confirms work of others [*17–19*], although differing from some of the earlier work carried out in this laboratory [*21*] and elsewhere [*15*]. However, far better separation of this fraction was achieved in this study, and this may account for the discrepancy.

The present work confirmed the absence of significant change in the values for the β-globulin fraction obtained in a previous study [*21*]. The fact that Bogdanowicz' [*15*] data were obtained in patients in an older age group and with a shorter duration of diabetes may account for the discrepancy between the results of his excellent study and those obtained consistently in this laboratory. The average age of all of Bogdanowicz' patients was fifty years, whereas that of our subjects was forty years. The average duration of diabetes in Bogdanowicz' patients was ten years; in our patients this was fifteen years for the entire group and twenty years if one considers only those with triopathy (retinopathy, neuropathy and nephropathy).

In most prior studies of changes in lipoproteins in diabetes the ultracentrifuge has been used and emphasis placed on changes in the β-lipoprotein or Gofman spectrum (S_f 0–400). Most recent work involving paper electrophoresis also has stressed the β-lipoproteins [*32*]. It is generally agreed that the β-lipoproteins are commonly elevated in diabetic persons with vascular complications. Relatively little study has been made previously of the α-lipoproteins. Although we recognized that the staining procedure used in our studies gave results of qualitative nature only, we hoped thereby to detect any change in the α-lipoprotein fraction. Our data suggest a trend toward a decrease in the α-lipoproteins, particularly in diabetic patients with the most extensive vascular complications. Following completion of this study Tolomelli et al. [*33*] reported that the alpha fraction was lower in twenty of thirty-eight diabetic patients with vascular complications, thus confirming the trend found in our investigations. Furthermore, the work of Barr and Russ [*34*], using a low temperature fractionation method, suggests that in some instances the α-lipoprotein values would be lower than normal, although in their study there was no attempt to correlate the apparent decrease with complications of diabetes.

There have been reports recently regarding the determination of the carbohydrate-containing proteins (or more literally, the protein-bound carbohydrates) by staining procedures after separation of the principal serum protein fractions by means of paper electrophoresis. The periodic acid-Schiff (PAS) stain has usually been employed following the original method introduced by Köiw [*30*] for use on paper. Since this procedure splits either two adjacent hydroxyl

TABLE IV

PROTEIN-BOUND CARBOHYDRATE CONTENT OF SERUM PROTEIN FRACTIONS

Case (no.)	Groups*	Albumin	Globulins					Total Area	
			α_1	α_2		β	γ	%	S.D.
				%	S.D.				
Components Expressed as Percentages of Total Planimeter Areas									
14	N	10.1	18.7	28.8	±2.28	22.3	19.1	...	.....
23	D_1	5.8	21.0	34.5	±5.30	24.4	14.2	...	.....
9	D_2	7.7	21.3	33.0	±3.40	22.7	15.1	...	.....
13	D_3	6.5	20.7	35.5	±4.88	22.9	13.6	...	.....
9	D_4	6.9	20.7	32.0	±2.80	24.6	16.3	...	.....
10	$D_{5,6}$	6.4	18.8	33.9	±3.86	23.7	15.8	...	.....
Planimeter Areas									
14	N	0.7	1.3	2.1	.....	1.7	1.4	7.4	±1.63
23	D_1	0.4	1.2	2.1	.....	1.4	0.9	6.2	±1.53
9	D_2	0.5	1.9	2.5	.....	2.0	0.8	8.3	±1.92
13	D_3	0.5	1.5	2.7	.....	1.7	1.0	7.8	±1.06
9	D_4	0.7	1.3	2.7	.....	1.6	1.2	7.4	±2.60
10	$D_{5,6}$	0.6	1.6	2.9	.....	1.8	1.5	8.9	±2.47

* For criteria of classification, see legend of Table II.

groups or one amino and one hydroxyl group within a carbohydrate chain, the hexosamine, non-hexosamine and pentose components of the polysaccharides attached to proteins should all stain well.

Calculations based on data in the literature obtained with chemical determinations for the protein-bound carbohydrates in different serum protein fractions gave the same relative percentages as were obtained in our and other laboratories [*35,36*] using the staining method directly on paper. After this study was completed an excellent investigation was reported comparing the staining method with direct analyses made on the corresponding fractions prepared by elution. The work of Björnesjö [*35*] and subsequent studies by Shetlar [*36*] suggest that the results of the PAS stain (given in sq. cm.) may be correlated with the total amount of protein-bound carbohydrate present in each fraction, but that the area of any given fraction or of the total electrophoretic curve cannot be quantitatively related to protein-bound carbohydrate. Therefore, this determination remains a qualitative procedure which gives a good indication of the relative amounts of protein-bound carbohydrates present in the fractions and, under carefully controlled conditions, an indication of changes that may occur in the serum.

The relative percentages of protein-bound carbohydrate in the fractions obtained from the serums of non-diabetic patients in this study are in good agreement with those obtained by others [*35,36*]. The increase in the total protein-bound carbohydrate (PAS stain) in the serums of diabetic persons with vascular complications corresponds to the work of Gilliland [*23*] and has been confirmed by recent work of Nervi et al. [*37*] and Polosa et al. [*38*], although Introzzi and Bernasconi [*39*] could find no such increase. The increase in the relative amounts of the protein-bound carbohydrate in the α_2-globulin fraction of diabetic persons with vascular complications corresponds to the work of Keiding [*17*], Gilliland et al. [*23*], and more recently of Polosa et al. [*38*]. Keiding [*17*] also showed that the protein-bound hexosamine content of the α_2-fraction is increased before vascular disease is clinically apparent, which confirms work to be discussed subsequently.

TABLE V
VALUES FOR α_2-GLOBULIN FRACTION OF SERUM PROTEIN IN PATIENTS WITH GOOD AND POOR CONTROL OF DIABETES

Poor Control		Good Control	
Case No.	α_2-globulin (gm. %)	Case No.	α_2-globulin (gm. %)
60	0.28	54	0.37
57	0.43	8	0.47
47	0.45	56	0.47
33	0.53	44	0.52
48	0.55	27	0.61
17	0.59	45	0.68
65	0.61	58	0.70
1	0.62	41	0.71
46	0.65	50	0.75
38	0.65	..	....
53	0.66	..	....
34	0.73	..	....
12	0.74	..	....
24	0.74	..	....
6	0.77	..	....
63	0.78	..	....
64	0.79	..	....
49	0.82	..	....
2	0.92	..	....
11	0.92	..	....
5	0.94	..	....
40	1.09	..	....
10	1.09	..	....
28	1.11	..	....
19	1.13	..	....
16	1.26	..	....
66	1.38	..	....

The one anomaly in the results presented here was a decrease in the areas representing the total protein-bound carbohydrate values in the serum of diabetic persons without vascular complications in contrast to absence of any change in the area of the α_2-fraction as compared with the normal mean. Thus the value for the relative percentage for the α_2-fraction was as high as that obtained for diabetic persons with vascular complications. Recently Orabona et al. [*40*] have shown that measurements of total non-hexosamine components in serum revealed values normal or slightly lower in forty-four subjects with uncomplicated diabetes. This work thus would support the lowered values for the total protein-bound carbohydrates in a similar group herein described.

In any consideration of serum protein changes in diabetic persons the question always arises as to the effect of control, age at onset, and duration. The data obtained for the α_2-globulin changes were analyzed to see if any correlation might be shown among these three factors. Of the sixty-four patients, an estimate of the degree of control could be made in only fifty-two, since the others were new patients in the clinic with inadequate past histories, newly discovered diabetic patients or patients who gave an inconsistent history so that no true estimate could be made of the over-all degree of control. In grouping the patients, twenty-seven had been in poor control (seven without complications), nine were in good control (three without complications) and the remainder (sixteen) were classed as in fair control. The data on the α_2-globulin fraction were then analyzed only for those persons in whom a clear-cut characterization of poor or good control could be made and in whom no non-diabetic complications were present. Table v shows the relationship of control to the changes in value for this fraction in these thirty-six persons. There appears to be an increase of the α_2-globulin fraction in the poor control group compared to that found in the good control group. The means were 0.75 and 0.59, respectively. The mean of the values for the good control group falls near that for the non-diabetic group (0.61). Furthermore, all seven of the diabetic persons without complications but with poor control had α_2-globulin values equal to or higher than the highest of all of the diabetic patients with good control irrespective of the presence of any diabetic complication. Thus there is some chemical evidence indicating that patients with diabetes without complications who are generally in poor control, but who have been in good control for several days at the time of the blood sampling show abnormal serum protein changes that are greater than all other patients with diabetes who are considered to be consistently well controlled.

Although the term "juvenile diabetic" is often applied to those with onset of diabetes prior to the age of fifteen, in terms of clinical application age of onset before age twenty may be a more practical definition. The data on the α_2 globulin change were analyzed to see if there appeared to be any difference between the so-called "juvenile" and "adult" case. The sixty-four cases studied here contained twenty-four "juveniles" and forty "adults." The mean α_2-globulin values were 0.83 and 0.68 gm. per cent respectively. In the group of diabetic

patients without complications nine of twenty-three were juvenile and the means for the α_2-globulin values were 0.80 and 0.72 gm. per cent respectively, indicating that age at onset for the two groups and the resultant physiological changes may play a role in the variations in the serum protein values.

Since one of the factors which could affect the protein fractions is the duration of diabetes, an attempt was made to find out if duration of the disease in the diabetic patients without complications (D-1) was influential. Since there were approximately equal numbers of patients with good, fair, poor and unknown control in this group (D-1), the choice of this group minimized the possible effects of control and of overt vascular changes as complicating factors in the analysis. A statistical analysis of the relationship of the absolute percentages (gm. per cent) for the α_2 globulin to the years' duration of diabetes did not show a statistical significant correlation of these factors (critical ratio = 1.87). However, both a scattergram and the trend coefficient r ($r = 0.897 \pm 0.48$) in conjunction with the high critical ratio (C.R.) indicated that there certainly was some relationship between protein changes and duration of diabetes. Perhaps the size of the group [*23*] together with the scattering of results prevented more accurate analysis. We would thus suggest that the abnormalities of the protein pattern tend to increase in a manner proportional to the duration of the disease even in the absence of clinically detectable vascular complications.

SUMMARY

1. The total proteins, lipoproteins and protein-bound carbohydrates of the blood serum were studied by means of paper electrophoresis in sixty-four patients with diabetes mellitus and in fourteen healthy non-diabetic persons.

2. In general, values for total protein in serum were lower in the diabetic person than in the non-diabetic subjects, the greatest decrease occurring in the serums of those patients with nephropathy. The principal changes in the serum protein fractions were in the albumin, α_2- and γ-globulin fractions. A decrease in albumin and gamma globulin values and an increase in the α_2 globulin values were roughly proportional to the extent of complications and were greatest in the patients with combined retinopathy, neuropathy and nephropathy.

3. Poor control, lower age at onset and longer duration of diabetes appeared to contribute to the increased α_2 globulin values found in diabetic persons without complications.

4. There was a tendency toward an increase in the β-lipoproteins, particularly in patients with nephropathy. The α-lipoproteins were lower in the patients with nephropathy as compared to other diabetic subjects.

5. Greater than normal amounts of protein-bound carbohydrates were found in the α_2-globulin fraction in the diabetic patients with complications, particularly in those with combined retinopathy, neuropathy and nephropathy.

REFERENCES

1. Bryfogle, T. W. and Bradley, R. The vascular complications of diabetes mellitus. *Diabetes*, 6: 159, 1957.
2. McManus, J. F. A. Development of intercapillary glomerulosclerosis. *Proc. Am. Diabetes A.*, 9: 303, 1949.
3. Friedenwald, J. S. Diabetic retinopathy. *Am. J. Ophth.*, 33: 1187, 1950.
4. Berkman, J., Rifkin, H. and Ross, G. The serum polysaccharides in diabetic patients with and without degenerative vascular disease. *J. Clin. Invest.*, 32: 415, 1953.
5. Jacobs, H. R. The bound glucosamine of serum mucoid in diabetes mellitus; fluctuations observed under the influence of insulin. *J. Lab. & Clin. Med.*, 34: 116, 1949.
6. Keiding, N. R. Protein-bound carbohydrates and proteins of serum from diabetic patients. Copenhagen, 1957. Monograph by C. Hamburgers Bogtrykkeri for Steno Mem. Hosp.
7. Keiding, N. R. and Tuller, E. F. Protein-bound carbohydrate in the serum of diabetic patients with and without vascular complications. *Diabetes*, 4: 37, 1955.
8. Mohnike, G. and Richter, H. Über den Eiweisszucker bei Diabetikern. I. *Ztschr. klin. Med.*, 151: 467, 1954.
9. Mohnike, G., Janert, H. and Richter, H. Über den Eiweisszucker bei Diabetikern. II. *Ztschr. klin. Med.*, 153: 114, 1955.
10. Nielsen, G. H. and Poulsen, J. E. The protein-bound carbohydrates in serum from diabetic patients and the relation to the duration of diabetes and the vascular complications. *Rep. Steno Mem. Hosp.*, 5: 71, 1953.
11. Tornblom, N. amd Nordstrøm, K. Serum polysaccharides and hyaline vascular changes in diabetes mellitus. *Acta endocrinol.*, 17: 426, 1954.
12. Engelberg, H., Gofman, J. and Jones, H. Serum lipid and lipoproteins in diabetic glomerulosclerosis. *Diabetes*, 1: 425, 1952.
13. Keiding, N. R., Mann, G. V., Root, H. F., Lawry, E. Y. and Marble, A. Serum lipoproteins and cholesterol levels in normal subjects and in young patients with diabetes in relation to vascular complications. *Diabetes*, 1: 434, 1952.

14. Tuller, E. F., Mann, G. V., Schertenleib, F., Roehrig, C. B. and Root, H. F. The effects of diabetic acidosis and coma upon the serum lipoproteins and cholesterol. *Diabetes*, 3: 279, 1954.
15. Bogdanowicz, G., Osinski, P. and Stein, F. Electrophorèse sur papier des proteines sériques au cours du diabète sucre et de ses complications. *Acta clin. Belg.*, 8: 585, 1953.
16. Führ, J. and Meinecke, R. Die klinische Bedeutung von Serum-Eiweissuntersuchungen bei Diabetikern. *Medizinische*, 2: 1677, 1953.
17. Keiding, N. R. Levels of serum protein fractions in diabetic patients with retinitis proliferans. *Proc. Soc. Exper. Biol. & Med.*, 86: 390, 1954.
18. Mellinghoff, K., Clossen, O., Kienitz, M. and von Wildemann, A. Untersuchungen über das Bluteiweissbild bei Diabetes mellitus. *Klin. Wchnschr.*, 29: 708, 1951.
19. Nostri, F. and D'Ermo, F. Sulle alterazioni della protidemia nei soggettik diabetici con retinopatia. *Boll. oculist.*, 33: 3, 1954.
20. Ralli, E. P., Barbosa, X., Beck, E. M. and Laken, B. Serum electrophoretic patterns in normal and diabetic subjects. *Metabolism*, 6: 331, 1957.
21. Schertenleib, F. and Tuller, D. F. Paper electrophoresis of serum proteins in diabetic patients. *Diabetes*, 7: 46, 1958.
22. Scheurlen, P. G. Über Serumeiweissveränderungen beim Diabetes mellitus. *Klin. Wchnschr.*, 33: 198, 1955.
23. Gilliland, J. C., Hanno, M. G. and Strudwick, J. I. Protein-bound polysaccharides in diabetes with and without complications. *Biochem. J.*, 56: 32, 1954.
24. Keiding, N. R. Levels of protein-bound hexosamine in serum and urine protein fractions from young diabetic patients with retinitis proliferans and diabetic nephropathy. *Rep. Steno Mem. Hosp.*, 6: 90, 1950.
25. Moinat, P., Scheidegger, J. J., Buzzi, C. and Berthoud, E. Réchèrche d'un desqéuilibre lipoproteique dans diverses affections par le lipidogramme et la fiche reticulo-endothelials. *Helvet. med. acta*, 22: 545, 1955.
26. Mehl, J. W. Biuret reaction of proteins in the presence of ethylene glycol. *J. Biol. Chem.*, 157: 173, 1945.
27. Grassmann, R. and Hannig, K. Ein quantitative Verfahren zur Analyze der Serumproteine durch Papierelektrophorese. *Ztschr. Physiol. Chem.*, 290: 1, 1952.
28. Peterson, J. Personal communication.
29. Moinat, P., Appel, W. and Tuller, E. F. A study of the determination of lipoproteins by paper electrophoresis. *Clin. Chem.* (In press.)
30. Köiw, E. and Gronwall, A. Staining of protein-bound carbohydrates after electrophoresis of serum on filter paper. *Scandinav. J. Clin. & Lab. Invest.*, 4: 244, 1952.
31. Root, H. F., Pote, W. H., Jr. and Frehner, H. Triopathy of diabetes. *Arch. Int. Med.*, 94: 931, 1954.
32. Baker, R. W. R., Joiner, C. L. and Trounce, J. R. A study by paper electrophoresis of the serum lipoproteins in diabetic and non-diabetic subjects. *Quart. J. Med.*, 24: 295, 1955.
33. Tolomelli, E., Vannini, P., Pellegini, R. and Barbora, L. Meaning of serum lipoprotein disequilibria in vascular complications of diabetes mellitus. *Arch. stud. fisiopat. e clin. ricambio*, 20: 196, 1956.
34. Barr, D. P., Russ, E. M. and Eder, H. A. Protein-lipid relationship in human plasma. II. In atherosclerosis and related conditions. *Am. J. Med.*, 11: 480, 1951.
35. Björnesjö, K. B. Staining of protein-bound serum polysaccharides in electrophoresis strips. *Scandinav. J. Clin. & Lab. Invest.*, 7: 153–159, 1955.
36. Shetlar, M. R., Cahill, C., Stidworthy, G. and Shetlar, C. L. Comparison of continuous and strip paper electrophoresis techniques for study of serum glycoproteins. *Proc. Soc. Exper. Biol. & Med.*, 93: 44, 1956.
37. Nervi, B. and De Pietra, G. Polysaccharides in diabetes mellitus with and without vascular complications. *Arch. stud. fisiopat. e clin. ricambio*, 20: 217, 1956.
38. Polosa, P. and Motta, L. Lipoproteins and glycoproteins in diabetes mellitus. *Arch. stud. fisiopat. e clin. ricambio*, 20: 220, 1956.
39. Introzzi, P. and Bernasconi, C. Behavior of serum proteins and of protein-bound carbohydrates and lipids in diabetic patients with and without vascular lesions. *Arch. stud. fisiopat. e clin. ricambio*, 20: 242, 1956.
40. Orabona, M. L., Mannino, N. and Giacovazzo, M. Serum mucopolysaccharides in diabetes with particular reference to diabetic vasculopathy. *Arch. stud. fisiopat. e clin. ricambio*, 20: 207, 1956.

Use of I^{131}-Labelled Fat in the Study of Lipid Handling in Patients with Coronary Artery Disease*

ROBERT H. SELLER, M.D.,† JONAS BRACHFELD, M.D., HERSCHEL SANDBERG, M.D. *and* SAMUEL BELLET, M.D.

Philadelphia, Pennsylvania

A RELATIONSHIP between abnormal lipid metabolism and atherosclerosis is generally accepted [*1–4*]. Elaborate laboratory methods, such as the ultracentrifugation [*3,4*], ethanol precipitation and electrophoresis of lipoproteins [*5,6*], the determination of phospholipids and total fats and other tests have been utilized to demonstrate this metabolic disturbance. There is much disagreement, however, as to the significance of these different lipid and lipoprotein measurements [*7,8*]. Lawry [*1*] concluded that the determination of total serum cholesterol remains the most practicable laboratory measurement for aiding in the identification of people with gross disturbances of lipid metabolism which predispose coronary heart disease. Doyle [*9*], Keys [*10*] and others have stated that the total serum cholesterol level provides as much, or as little, information as more elaborate and difficult chemical procedures.

It has been shown by many workers that in all these tests there is considerable overlap between the values found in normal subjects and in those with atherosclerosis [*11,12*]. While the differences between the two groups may be statistically significant, they are of limited clinical usefulness in certain patients; as is well known, many patients who have had a myocardial infarction have normal serum levels of cholesterol and other lipid fractions.

Another approach to the elucidation of this metabolic disturbance has been the determination, after a fatty meal, of serum lactescence [*13–15*], various lipid fractions [*16–18*], and coagulation factors [*17,20–22*]. Here again these methods have not proved reliable in differentiating a given individual with coronary heart disease from normal subjects. A relatively new approach to this problem has been by use of fat labelled with radioisotopes, hitherto used primarily in the study of various malabsorption syndromes [*23–28*] such as pancreatic insufficiency, sprue and obstructive jaundice, in which low levels of radioactivity have been noted in the blood. Thannhauser and Stanley [*29,30*] fed I^{131}-labelled olive oil to patients and noted high levels of radioactivity in the blood of patients with nephrosis and idiopathic hyperlipemia. Likoff and associates [*31*] have reported that after the administration of a fat meal containing I^{131}-labelled glyceryl trioleate, abnormally elevated levels of radioactivity appeared in the blood of patients with atherosclerosis. They used Ruffin's technic [*26*] in which Tween 80,® a surface active agent, is added to the test meal, which contains approximately 90 gm. of fat.

Our study was undertaken to evaluate further the usefulness of an I^{131}-tagged fat meal in the study of patients with atherosclerosis, specifically coronary heart disease. For reasons which will be discussed later, a somewhat different technic was employed.

METHODS AND MATERIALS

The subjects employed in this study consisted of fifty-one normotensive male patients of the Philadelphia General Hospital. Approximately equal numbers of outpatients were utilized. Patients with cancer, gastrointestinal disease or chronic debilitating illness

* From the Division of Cardiology, Philadelphia General Hospital, and the Robinette Foundation, University of Pennsylvania, Philadelphia, Pennsylvania. This work was aided by a grant from the U. S. Public Health Service, (141 C7) and the Eli Lilly Company, Indianapolis, Indiana.

† Research Fellow of the Heart Association of Southeastern Pennsylvania.

were excluded. The age range was nineteen to fifty-three years, forty-six of the fifty-one patients being between the ages of twenty and fifty. An attempt was made to compare patients of comparable ages.

The control group consisted of twenty normal subjects ranging in age from nineteen to fifty-three years. They had no manifestations of coronary heart disease as determined by history, physical examination and electrocardiogram. Individuals who were grossly overweight or had serum cholesterol values greater than 240 mg. per cent were not included in the normal control group.

There were twenty-one abnormal subjects, ranging in age from twenty-seven to fifty-two years. All had documented electrocardiographic evidence of previous myocardial infarction. All but two gave a history of a myocardial infarction having occurred from seven years to two months prior to the test. In these two subjects the electrocardiogram and vectorcardiogram provided unequivocal evidence of an old myocardial infarction.

A third heterogeneous group consisted of ten patients who displayed no evidence of myocardial infarction, but the presence of other abnormalities precluded their incorporation in the normal group. These abnormalities were serum cholesterol levels of 240 mg. per cent or more (five patients), marked obesity (four patients), and intermittent claudication (one patient). Such subjects are known to have a higher incidence of atherosclerosis and coronary artery disease than a normal control group [*32,33*].

The method employed in this test was a modification of the Beres technic [*23*]. For the three days preceding the study, patients received 20 drops of Lugol's solution daily to prevent uptake of the I^{131} by the thyroid gland. After a twelve-hour overnight fast, venous blood samples were drawn to determine serum cholesterol, lipid phosphorus, and alpha and beta lipoproteins. These values were obtained by standard methods [*5,34,35*]. At 9:00 A.M. the patient was given the test meal from a 600 cc. beaker containing 100 microcuries of raolein (Abbott Laboratories) stock solution* in 15 cc. of olive oil, 100 cc. of grade B homogenized milk and 100 cc. of ginger ale. The beaker was then rinsed with 40 cc. of milk, rerinsed with 100 cc. of milk, then rinsed once again with 100 cc. of ginger ale. Each rinse was given to the patient. (Raolein is a glyceryl trioleate which has been labelled with I^{131} by the addition of I^{131}-monochloride to one of the double bonds of the fatty acid.)

Starting with lunch (12:30 P.M.) the patients were allowed to consume their usual diet. Venous blood samples (10 cc.) were drawn at two, four, six, eight and twenty-four hours after administration of the test meal. They were placed in oxalated tubes and refrigerated. The urine was collected for twenty-four hours in containers to which potassium iodide and toluene had been added. The patients also received 10 drops of Lugol's solution daily for five days following the test.

The blood samples and urine were assayed for radioactivity in the following manner: the radioactivity of the whole blood and of the fraction precipitated by trichloracetic acid (TCA) was determined for all blood samples. Three milliliters of oxalated blood was pipetted into duplicate dry test tubes. One of these tubes served as the whole blood sample. To the other tube 1 cc. of 1 per cent potassium iodide was added and, after mixing thoroughly, 10 cc. of 20 per cent TCA was added. The mixture was stirred and allowed to stand for thirty minutes. The mixture was then resuspended, centrifuged at 20,000 r.p.m. for three minutes and the supernatant decanted. Next, the precipitate was washed with 5 per cent TCA, resuspended and centrifuged two times. In each instance the supernatant was discarded. The TCA precipitate and whole blood sample were then counted in a well-type scintillation counter and compared to an aliquot of the control solution. The values obtained for the whole blood and TCA precipitated samples were multiplied by the blood volume. (Blood volume was estimated at 7.7 per cent of the body weight in kilograms [*36*] except in four grossly overweight patients (Table 1) in whom it was estimated as 32.9 cc./cm. height [*37*].) These figures, the total amount of I^{131} radioactivity present in the whole blood and TCA precipitable fractions, were then calculated as per cent of ingested dose.* A 3 cc. sample of the twenty-four-hour urine collection was also assayed and compared with the control in order to determine the per cent of ingested dose* excreted in the urine.

In sixteen patients the blood volume was subsequently measured directly by the use of radioactive iodinated human serum albumin [*38*].

Side Effects. A macular eruption developed in one patient and swelling of the salivary glands developed in another when Lugol's solution was administered prior to the test meal. Both disappeared spontaneously within a few days. One patient became nauseated and vomited shortly after ingestion of the test meal, and was not included in the series.

RESULTS

Normal Control Group. Following the test meal there was a progressive rise in radioactivity in the whole blood (WB) and the trichloracetic acid (TCA) precipitated samples, with peak levels usually at four or six hours. The radio-

* Raolein, when received at the laboratory, was diluted with olive oil to a concentration of 10 to 15 microcuries per cc. An aliquot of this stock solution, diluted 1:1000 with petroleum ether, served as control.

* Ingested dose equals the administered dose of I^{131} (100 microcuries) minus the amount left in the 600 ml. beaker.

TABLE I

HETEROGENEOUS GROUP

Patient	Age (yr.)	Race	Height (in.)	Weight (lb.)	Fasting Serum				I^{131} Radioactivity* (% of ingested dose)					Remarks†	Abnormal Lipid Handling Test
					Lipoproteins (% alpha)	Lipoproteins (% beta)	Lipid Phosphorus (mg. %)	Cholesterol (mg. %)	24 hr. Urine	$WB^{p,t}$	$TCA^{p,t}$	WB^{24}	TCA^{24}		
Intermittent Claudication and Hypercholesteremia															
J. M.	34	W	68.5	184	13.6	86.4	9.7	252	74	17.2‡	(8.9‡)	(7.8)	(2.2)	RISA	+
Hypercholesteremia															
F. H.	51	C	66.5	160	13.9	86.1	9.3	263	66	13.3	4.5	3.0	.52	RISA	
R. M.	38	C	73	184	14.8	85.2	11	321	65	20.9‡	12.2‡	4.8	1.8	RISA	+
H. H.	33	C	76	176	15.9	84.1	10.8	261	50	19.5‡	10.4‡	4.8	.61	RISA	+
J. T.	33	C	68	168	18.2	81.8	9.9	240	50	13.3‡	8.8‡	2.2	.64		+
J. H.	30	C	68	178	9.2	90.8	9.2	276	32	7.4‡	4.4‡	1.6	.30		
Marked Obesity															
A. C.	43	W	73	221	16.4	83.6	10.1	156	67	17.2‡	11.4‡	3.8	2.0		+
J. P.	40	W	72.5	220	18.7	81.3	9.4	208	58	13.6‡	5.2‡	3.8	1.7	Father-gout RISA	+
D. L.	32	W	75.5	260	21.9	78.1	12.5	247	50	9.4‡	3.1‡	2.8	.47	RISA	
J. B.	31	C	77.5	230	24.3	75.7	10.8	121	53	19.8‡	13.96‡	4.3	2.4		+

* $WB^{p,t}$ = the highest level of radioactivity attained in the whole blood and the time (t) of sample in which it occurred.
$TCA^{p,t}$ = the highest level of radioactivity attained in the TCA precipitable fraction and the time (t) of sample in which it occurred.
WB^{24} = level of radioactivity in whole blood at twenty-four hours.
TCA^{24} = level of radioactivity in the trichloracetic acid precipitable fraction at twenty-four hours.
† RISA = Radio iodinated serum albumin determination of blood volume.
‡ These figures represent values 2 or more standard deviations above the mean levels of the central group.

activity contained in the whole blood and the TCA precipitable fraction at peak time (WB^p, TCA^p) and at twenty-four hours (WB^{24}, TCA^{24}) are shown in Table II. These figures are reported as the calculated circulating I^{131} radioactivity expressed as the percentage of ingested dose.

The mean values of the twenty "normals" were: WB^p, 11.0; TCA^p, 4.5; WB^{24}, 2.9; TCA^{24}, 0.6. (Table III.) Of the twenty subjects in this control group, the results in two were abnormal. (Table II.) In all the patients studied the criterion for an abnormal result was that one or more of the four values (WB^p, TCA^p, WB^{24}, TCA^{24}) exceeded the corresponding mean normal value by two or more standard deviations. (Table IV.) In most of the abnormal subjects, two or three of these values exceeded their corresponding normal means by two or more standard deviations.

Group with Myocardial Infarction. Here again peak levels usually occurred at four or six hours. The individual patient's values (WB^p, TCA^p, WB^{24}, TCA^{24}) are shown in Table V. The mean values for this group were: WB^p, 19.9; TCA^p, 10.0; WB^{24}, 4.9; TCA^{24}, 1.6. (Table III.) All twenty-one patients in this group had an abnormal response to the test.

The mean values (WB^p, TCA^p, WB^{24}, TCA^{24}) of the twenty normal subjects were considerably lower than those obtained in the twenty-one patients with coronary artery disease. There was little overlap and a high degree of separation. The differences between the means of the normal subjects and those of the group with myocardial infarction were statistically highly significant. The value of P was less than 0.0005.* (Table III.) The probability of such large dif-

* If there is *no* difference between the means of the normal control group and the means of the group with myocardial infarction, then the probability of getting such large differences, in samples of this size, is less than 5 in 10,000.

TABLE II

NORMAL CONTROL GROUP

Patient	Age (yr.)	Race	Height (in.)	Weight (lb.)	Fasting Serum				I^{131} Radioactivity* (% of ingested dose)					Remarks†	Abnormal Lipid Handling Test
					Lipoproteins (% alpha)	Lipoproteins (% beta)	Lipid Phosphorus (mg. %)	Cholesterol (mg. %)	24 Hr. Urine	WB^{p_t}	TCA^{p_t}	WB^{24}	TCA^{24}		
A. C.	53	W	70	117	16.7	83.3	5.1	157	54	10.2^{6}	2.4^{6}	2.4	.71	RISA	..
J. T.	52	C	65	138	24.1	75.9	10	231	21	8.4^{3}	4.3^{3}	**6.0**†	**1.6**		+
W. C.	49	C	63.5	132	16.7	83.3	5.2	145	38	12.6^{8}	3.88^{9}	2.9	.40	RISA	..
J. C.	44	W	67	137	25.8	74.2	9.8	231	45	12.17^{4}	5.65^{4}	1.98	.29	.....	..
W. J.	39	C	68	148	31.7	68.3	7.3	184	50	16.27^{3}	**8.9**‡	3.9	.93	.....	+
H. J.	37	C	75	150	21.9	78.1	7.1	187	66	13.1^{4}	4.7^{4}	.92	.48	RISA	..
M. R.	37	C	68.5	146	15.6	84.4	9.4	205	36.1	12.8^{4}	4.8^{4}	2.17	.39	Mother-D	..
H. T.	37	C	66.5	125	19.3	80.7	9.4	211	77	13.2^{2}	5.8^{2}	.92	.33	RISA	..
E. B.	36	C	70	150	40	60	7.5	138	87	12.2^{8}	5.1^{8}	2.6	.96	RISA	..
H. M.	35	C	75	145	24.4	75.6	8.5	198	46	9.19^{4}	3.7^{8}	3.96	.44	.....	..
L. D.	34	C	67	135	25.4	74.6	6.9	124	32	10.3^{4}	4.5^{4}	3.5	1.20	.....	..
F. C.	31	C	71	184	28.2	71.8	6.9	143	66	14.8^{4}	4.2^{4}	3.2	.45	.....	..
M. C.	29	W	65.5	148	25.7	74.3	6.6	179	33	8.5^{4}	3.74^{4}	1.3	.30	.....	..
C. W.	28	C	69.5	155	29.3	70.7	10.4	190	69	12.8^{4}	5.16^{4}	2.37	.40	.....	..
S. K.	27	W	67	143	29.6	70.4	7.2	124	41	7.8^{4}	3.8^{4}	2.5	.42	.....	..
T. B.	26	W	64	145	8.1	91.9	8.4	121	45	6.9^{4}	3.3^{4}	1.0	.20	.....	..
D. T.	24	W	73	148	25.8	74.2	6.8	137	52	9.3^{3}	2.43^{3}	5.75	1.24	.....	..
W. B.	22	C	67.5	123	17.8	82.2	7.1	154	43	10.95^{4}	3.67^{4}	2.46	.47	.....	..
G. T.	22	C	73.5	185	14.1	85.9	7.8	184	79	12.8^{4}	3.4^{2}	1.96	.33	Father-D	..
T. W.	19	C	73	149	16.7	83.3	8.2	183	50	15.0^{4}	6.71^{4}	5.3	.87	.....	..

* WB^{p} = the highest level of radioactivity attained in the whole blood and the time (t) of sample in which it occurred.
TCA^{p_t} = the highest level of radioactivity attained in the TCA precipitable fraction and the time (t) of sample in which it occurred.
WB^{24} = level of radioactivity in whole blood at twenty-four hours.
TCA^{24} = level of radioactivity in the trichloracetic acid precipitable fraction at twenty-four hours.
† RISA = radio iodinated serum albumin determination of blood volume.
D = diabetic.
‡ These figures represent values 2 or more standard deviations above the mean levels of the control group.

ferences being due to chance is less than 5 in 10,000.

Heterogeneous Group. In this group of patients (Table I) abnormal results were obtained in three of five subjects with hypercholesteremia (240 mg. per cent or more), three of the four markedly obese patients, and in the one patient with intermittent claudication.

COMMENTS

The Use of Raolein in the Study of the Disposition of Lipid. Although many details of lipid transport and metabolism are still ill defined, somewhat controversial, and beyond the scope of this paper, evidence from several sources seems to confirm the validity of using raolein as a tracer of neutral fat metabolism [*39–41*]. Beres has shown that more than 95 per cent of the I^{131}-labelled fat in this test is absorbed in patients without malabsorptive diseases. It has also been demonstrated that the I^{131} fatty acid bond is stable to gastric juice, bile, pancreatic juice, and 20 per cent TCA. This bond is apparently broken in the process of fat utilization [*23*].

In this test, a whole blood sample and the fraction precipitated by TCA were counted for radioactivity. It has been determined that the radioactivity in the TCA precipitate is contained

TABLE III
CIRCULATING I^{131} RADIOACTIVITY
(PERCENTAGE OF INGESTED DOSE)

	Normal Control Group (20) Mean	Group with Myocardial Infarction (21)	Difference between Means	Level of Significance (p less than)
Whole blood^{P}	11.0	19.9	7.1	0.0005
TCA^{P}	4.5	10.0	5.5	0.0005
Whole blood^{24}	2.9	4.9	2.0	0.0005
TCA^{24}	0.6	1.6	1.0	0.0005

TABLE IV
NORMAL CONTROL GROUP
CIRCULATING I^{131} RADIOACTIVITY
(PERCENTAGE OF INGESTED DOSE)

	Mean ± S.D.	Mean Plus 2 S.D.
Whole blood^{P}	11 ± 3.5	17.9
TCA^{P}	4.5 ± 1.5	7.4
Whole blood^{24}	2.9 ± 1.5	5.8
TCA^{24}	0.6 ± 0.37	1.4

primarily in the lipid fraction of lipoproteins [*23,42*]. It has also been shown that the activity in the TCA supernatant (whole blood activity minus TCA activity) is not part of a lipid or protein moiety. The level of radioactivity in this TCA supernatant is influenced by the rate of fat breakdown, the renal clearance of inorganic I^{131}, and the completeness of thyroid blockage. The lipid-bound I^{131} activity found in the TCA precipitated fraction is influenced by the rate of absorption as well as the rate of utilization [*23*].

A specific interpretation of the relationship between the activity contained in the TCA precipitable fraction and that contained in the supernatant is not possible at this time. However, it is of interest that the ratio of peak TCA activity to peak supernatant activity (WB^{P} minus TCA^{P}) is significantly higher in the patients with abnormal responses. The mean value of $\frac{TCA^{P}}{WB^{P} - TCA^{P}}$ was 0.69 for the control group and 1.56 for the myocardial infarction group.

Special Features of This Study. Many investigators have shown that in other fat meal and lipid tests much overlap exists between the values found in normal subjects and in patients with coronary heart disease [*7,8,10,11*]. In this test the differences between the mean values of the control group and of the patients with myocardial infarction are very significant statistically. Even more striking is the fact that the results of this test have been consistently abnormal in *every* patient with a proved myocardial infarction although many had normal serum levels of cholesterol, lipid phosphorus and alpha and beta lipoproteins. It was consistently abnormal even in the few atherosclerotic patients (Table v) who had received "hypocholesteremic therapy" in the form of a linoleic acid supplement to their diet. Long term observation may determine the significance of the abnormal tests demonstrated by two subjects (J. T. and W. J.) in the control group. (Table II.)

An attempt was made to compare normal and abnormal (group with myocardial infarction) subjects in corresponding age groups in order to obviate results which might be caused by aging. (Table VI.) On statistical analysis there was no significant relationship between age and test values among the normal or among the abnormal group. In addition, there was no significant correlation between weight and test values in the control group or in the group with myocardial infarction. This is illustrated in Figure 1 which shows a typical normal and a typical abnormal curve obtained in two subjects of comparable age and physique. Both had normal serum cholesterol levels. The abnormal subject had electrocardiographic and vectorcardiographic evidence of a myocardial infarct. At four hours the radioactivity in the WB and TCA fraction of the abnormal subject (R. D.), was considerably greater than that found in his normal counterpart (H. M.). Figure 2 shows the curve of another young patient (J. M.), a thirty-four year old white man, with intermittent claudication, absent pedal pulses and an elevated serum cholesterol level.

The use of a radioactive labelled fat, raolein, in this test meal obviated the administration of an unphysiologic heavy loading dose of fat. The test meal contained 370 calories: 9 gm. of protein, 33 gm. of carbohydrate, and only 24 gm. of fat. This is approximately equivalent to two slices of toast and butter, and 8 ounces of grade B milk [*43*].

No Tween or other surface active agent was used, such as has been employed by some investigators [*26,37*]. These agents are known to affect

TABLE V

GROUP WITH MYOCARDIAL INFARCTION

Patient	Age (yr.)	Race	Height (in.)	Weight (lb.)	Fasting Serum				I^{131} Radioactivity* (% of ingested dose)					Remarks†	Abnormal Lipid Handling Test
					Lipoproteins (% alpha)	Lipoproteins (% beta)	Lipid Phosphorus (mg. %)	Cholesterol (mg. %)	24 Hr. Urine	WB^{pt}	TCA^{pt}	WB^{24}	TCA^{24}		
J. A.	52	W	68	180	16.8	83.2	12.4	238	45	16.9[6]	**8.3[6]‡**	4.1	1.1	.....	+
L. Y.	51	W	68	175	16.0	84.0	9.5	240	63	17.5[4]	**13.9[4]**	5.2	**2.7**	.....	+
E. C.	49	W	72	201	12.3	87.7	8.7	225	56	15.9[6]	**8.5[6]**	4.8	**1.5**	.....	+
L. R.	48	W	68	185	....	....	....	...	33	**18.7[4]**	**10.3[4]**	2.3	.9	RISA Mother-D	+
E. D.	48	W	68	160	12.7	87.3	12.0	343	43	17.7[4]	**8.9[4]**	3.8	.5	I.C.	+
R. Da.	48	W	71	177	30.8	69.2	12.7	293	58	17.1[4]	**10.9[4]**	**6.6**	**1.7**	.....	+
W. M.	47	W	68	172	18.4	81.6	12.4	237	62	**22.2[4]**	**15.6[4]**	3.9	1.2	.....	+
J. H.	47	W	68.5	164	17.5	82.5	7.0	97	51	13.8[4]	**7.8[4]**	4.6	**2.1**	.....	+
S. L.	47	W	68	165	15.4	84.6	8.0	167	61	15.6[4]	10.2[4]	4.4	**2.2**	.....	+
F. T.	45	W	68	185	17.6	82.4	12.4	175	61	10.9[6]	3.5[6]	**6.9**	**2.5**	.....	+
A. P.	44	W	69	200	....	....	....	...	44	.....	.....	**6.0**	**1.8**	Mother-D RISA	+
D. F.	44	W	71	199	18.5	81.5	7.6	229	69	17.5[6]	**8.0[6]**	4.8	**1.4**	xanthelasma	+
J. F.	42	W	68	176	13.5	86.5	13.1	242	50	16.1[6]	**7.3[6]**	**6.6**	**1.5**	xanthelasma	+
R. C.	41	W	70	180	13.7	86.3	10.7	237	56	**24.7[6]**	**14.4[6]**	**6.4**	.5	.....	+
J. S.	41	W	69	172	....	....	....	...	61	**19.5[4]**	**10.6[4]**	2.0	**1.8**	I.M.L.	+
J. M.	41	W	68	182	....	....	....	...	44	.....	.....	**7.5**	**2.2**	.....	+
E. M.	38	W	69	195	20.2	79.8	8.5	182	52	5.82[6]	3.5[6]	4.3	**1.6**	RISA	+
D. D.	37	C	67	148	18.2	81.8	8.6	224	64	**19.8[4]**	**14.1[4]**	3.25	**2.65**	RISA	+
J. B.	35	C	67	172	14.4	85.6	11.6	197	54	**21.5[4]**	**9.7[4]**	5.1	.7	.....	+
R. D.	33	C	67	160	14.0	86.0	13.1	219	63	**23.3[4]**	**14.9[4]**	4.1	1.3	RISA	+
A. S.	27	W	72	204	20.7	79.3	9.5	153	..	11.3[4]	**8.1[4]**	5.5	**2.5**	RISA	+

* WB^{pt} = the highest level of radioactivity attained in the whole blood and the time (t) of sample in which it occurred.
TCA^{pt} = the highest level of radioactivity attained in the TCA precipitable fraction and the time (t) of sample in which it occurred.
WB^{24} = level of radioactivity in whole blood at twenty-four hours.
TCA^{24} = level of radioactivity in the trichloracetic acid precipitable fraction at twenty-four hours.
† RISA = radio iodinated serum albumin determination of blood volume.
D = diabetic.
I.C. = intermittent claudication.
I.M.L. = internal mammary ligation.
‡ These figures represent values 2 or more standard deviations above the mean levels of the control group.

fat absorption [*23,44*] and are occasionally used therapeutically to facilitate fat absorption. When given parenterally, they may modify the action of lipoprotein lipase [*45,46*].

As mentioned previously, an estimate of blood volume was used in the calculation of the circulating I^{131} radioactivity. There is little agreement as to the most reliable method of estimating blood volume. Most investigators believe that estimates based on 7.7 per cent of body weight in kilograms or based on the surface area provide an acceptable approximation except in markedly obese patients, in whom estimates based on height are more reliable [*37*]. In this study blood volume was usually estimated in this manner. In sixteen patients studied (five "normals," five with myocardial infarctions, three with hypercholesteremia, two with gross obesity and one with intermittent claudication and an elevated serum cholesterol) the blood volumes

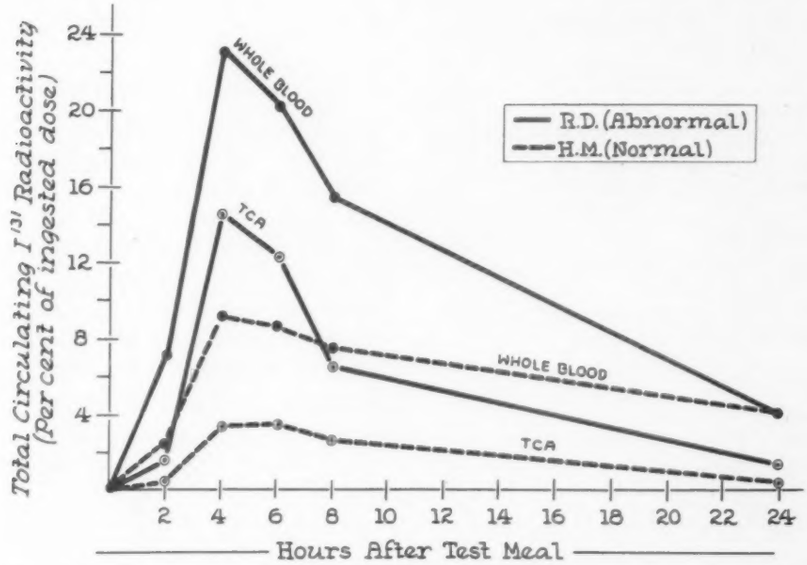


FIG. 1. H. M., typical normal curve in a thirty-five year old Negro man (weight, 145 pounds; serum cholesterol, 198 mg. per cent; electrocardiogram, normal). Note the peak levels at four hours. R. D., typical abnormal curve in a thirty-three year old Negro man with a healed inferior myocardial infarction (weight, 160 pounds; serum cholesterol, 219 mg. per cent). Note markedly elevated levels at peak time, but only slightly elevated levels at twenty-four hours.

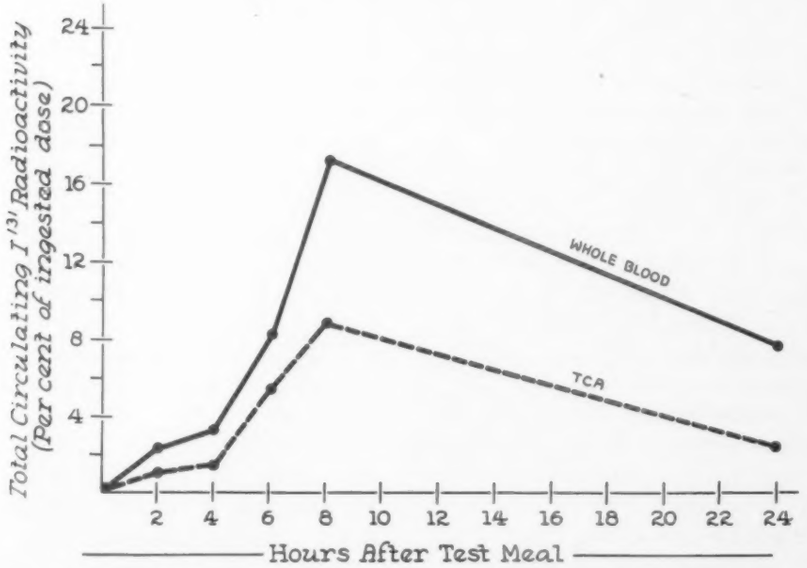


FIG. 2. J. M., markedly abnormal curve obtained in a thirty-four year old white man with intermittent claudication (weight, 184 pounds; serum cholesterol, 252 mg. per cent; electrocardiogram, normal).

were measured more directly using radioiodinated serum albumin (Abbott Laboratories) in order to check the validity of the estimated blood volumes. Estimates based on weight were most accurate in the majority of these patients except in the two grossly obese patients in whom the estimate based on height was found to be more accurate. In these sixteen patients the normality or abnormality of the response to the lipid test was not affected by the blood vol-

TABLE VI
AGE DISTRIBUTION OF SUBJECTS TESTED

Group and Result	Number of Patients				
	19–25 Years	26–35 Years	36–45 Years	46–53 Years	Total
Control group: Normal results	4	7	5	2	18
Control group: Abnormal results	..	..	1	1	2
Group with myocardial infarction: Normal results	..	..	..	..	None
Group with myocardial infarction: Abnormal results	..	3	9	9	21
Heterogeneous group: Normal results	..	2	..	1	3
Heterogeneous group: Abnormal results	..	4	3	..	7

ume as determined by different methods (height 32.9 cc./cm.; surface area = 3,122 cc./M^2 [*37*]; weight, 0.77 cc./gm. [*33*] or radioiodinated serum albumin [*38*]).

Interpretation and Possible Applications of this Test. At the present time, the exact composition of the various fractions (WB^p . . . TCA^p) which contain the radioactivity is not known, thus precluding any definitive interpretation of the abnormality detected by this test. There are several factors which might underlie this metabolic disturbance. They include the size of the metabolic pools in which the lipid-bound I^{131} and free I^{131} are distributed [*48,49*], the rate of lipid catabolism and fatty acid oxidation [*50*], the rate of lipid synthesis [*51*] and possible enzymatic deficiencies.

Although the precise defect cannot be delineated, if the consistently abnormal results of this test in patients with myocardial infarction (Table v) and if the results (Table III) obtained in our series are confirmed in subsequent studies, the test would be of considerable clinical interest. The use of this test in conjunction with technics of lipoprotein separation and other tests might aid in the elucidation of the metabolic disturbance in atherosclerosis and coronary heart disease. It would be of interest to utilize this test in a large prospective study, with long term follow-up, in order to correlate the abnormal findings with the subsequent development of coronary atherosclerosis. Finally, the test might be of value in determining the efficacy of therapeutic agents and regimens.

SUMMARY

In order to study the handling or disposition of lipid in patients with coronary artery disease, fifty-one normotensive male subjects between the ages of nineteen and fifty-three received a test meal which contained a small amount of radioactive I^{131}-labelled glyceryl trioleate. Serial blood samples were drawn after the test meal in order to determine the total circulating radioactivity contained in the whole blood and in the trichloroacetic acid precipitable fraction. These were reported as percentage of ingested dose. The series included twenty "normal" subjects and twenty-one patients, of comparable ages, with documented myocardial infarctions.

At peak time and at twenty-four hours the differences between the mean levels of radioactivity obtained in the control group and those obtained in the group with myocardial infarction were statistically highly significant ($p < 0.0005$). There was little overlap and a high degree of separation. An abnormal response to the test was demonstrated in every patient who had had a myocardial infarction although many of these patients had normal serum levels of cholesterol, lipid phosphorus, and alpha and beta lipoproteins. There was no significant relationship between test values and age or weight among the control group or among the group with myocardial infarction.

Ten patients with abnormalities such as hypercholesteremia, marked obesity and intermittent claudication were also studied and the data are presented.

The clinical significance and possible applications of this test are discussed.

Acknowledgment: We wish to express our appreciation to Lawrence E. Meltzer, M.D., Philadelphia General Hospital, for referring some of his patients for this study and to Dr. Stanley S. Schor, Associate Professor of Statistics, University of Pennsylvania, for his assistance in the statistical analysis of this study. The technical assistance of Wayne A. Meyers, Radiologic Physicist, Philadelphia General Hospital, is also gratefully acknowledged.

REFERENCES

1. LAWRY, E. Y., MANN, G. V., PETERSON, A., WYSOCKI, A. P., O'CONNELL, R. and STARE, F. J.

Cholesterol and beta lipoproteins in the serums of Americans: well persons and those with coronary heart disease. *Am. J. Med.*, 22: 605, 1957.

2. Page, I. H. Some aspects of the nature of the chemical changes occurring in atheromatosis. *Ann. Int. Med.*, 14: 1741, 1941.
3. Gofman, J. W., Jones, H. B., Lindgren, F. T., Lyon, T. P., Elliott, H. A. and Strisower, B. Blood lipids and human atherosclerosis. *Circulation*, 2: 161, 1950.
4. Gofman, J. W., Glazier, F., Tamplin, A., Strisower, B. and De Lalla, O. Lipoproteins, coronary heart disease and atherosclerosis. *Physiol. Rev.*, 34: 589, 1954.
5. Durrum, E. L., Paul, M. H. and Smith, E. R. B. Lipid detection in paper electrophoresis. *Science*, 116: 428, 1952.
6. Langan, T. A., Durrum, E. L. and Jencks, W. P. Paper electrophoresis as a quantitative method: measurement of alpha and beta lipoprotein cholesterol. *J. Clin. Invest.*, 34: 1427, 1955.
7. Engelberg, H. Diagnosis of atherosclerosis. I. Correlation between clinical diagnosis, serum cholesterol and low-density lipoproteins and resting and exercise electrocardiograms. *Am. J. Cardiol.*, 1: 315, 1958.
8. Clough, P. W. Editorial. The value of determinations of cholesterol and of lipoproteins of low density in the blood as predictors of overt atherosclerosis. *Ann. Int. Med.*, 47: 841, 1957.
9. Doyle, J. T. Serum proteins in preclinical and in manifest ischemic heart disease. *J. Chron. Dis.*, 6: 33, 1957.
10. Keys, A. Atherosclerosis: a problem in newer public health. *J. Mt. Sinai Hosp.*, 20: 118, 1953.
11. Krause, S. Coronary artery disease—present concepts. *Am. J. Cardiol.*, 1: 334, 1958.
12. Barr, D. P., Russ, E. M. and Eder, H. A. Protein-lipid relationships in human plasma. II. In atherosclerosis and related conditions. *Am. J. Med.*, 11: 480, 1951.
13. Pomeranze, J., Bienfield, W. H. and Chessin, M. Serum lipid and fat tolerance studies in normal, obese and atherosclerotic subjects. *Circulation*, 10: 742, 1954.
14. Schwartz, L., Woldow, A. and Dunsmore, R. A. Determination of fat tolerance in patients with myocardial infarction. *J. A. M. A.*, 149: 364, 1952.
15. Woldow, A., Chapman, J. E. and Evans, J. J. Fat tolerance in subjects with atherosclerosis: heparin effects upon lipemia, lipoproteins and gamma globulin. *Am. Heart J.*, 47: 568, 1954.
16. Zinn, W. J. and Griffith, G. C. A study of serum fat globules in atherosclerotic and non-atherosclerotic male subjects. *Am. J. M. Sc.*, 220: 597, 1950.
17. Barritt, D. W. Alimentary lipaemia in men with coronary artery disease and in controls. *Brit. M. J.*, 2: 640, 1956.
18. Kuo, P. T., Joyner, C. R. and Reinhold, J. G. Effects of fat ingestion and heparin administration on serum lipids of "normal" hypercholesteremic, hyperlipemic and atherosclerotic subjects. *Am. J. M. Sc.*, 232: 613, 1956.
19. Kuo, P. T. and Joyner, C. R., Jr. Angina pectoris induced by fat ingestion in patients with coronary artery disease. *J. A. M. A.*, 158: 1008, 1955.
20. Swank, R. L. Effect of fat on blood viscosity in dogs. *Circulation Res.*, 4: 579, 1956.
21. Robinson, D. S. and Poole, J. C. F. The similar effect of chylomicra and ethanolamine phosphatide on the generation of thrombin during coagulation. *Quart. J. Exper. Physiol.*, 41: 36, 1956.
22. Borrero, J., Sheppard, E. and Wright, I. S. Further experiences with blood coagulation after fat meals and carbohydrate meals. *Circulation*, 17: 936, 1958.
23. Beres, P., Wenger, J. and Kirsner, J. B. The use of I^{131} triolein in the study of absorptive disorders in man. *Gastroenterology*, 32: 1, 1957.
24. Berkowitz, D. and Sklaroff, D. The use of radioactive fat in the study of absorption in various disease states. *Arch. Int. Med.*, 100: 951, 1957.
25. Shingleton, W. W., Baylin, G. J., Isley, J. K., Sanders, A. P. and Ruffin, J. M. The evaluation of pancreatic function by use of I^{131} labelled fat. *Gastroenterology*, 32: 28, 1957.
26. Ruffin, J. M., Shingleton, W. W., Baylin, G. J., Hymans, J. C., Isley, J. K., Saunders, A. R. and Sohmer, M. F. I^{131} labelled fat in the study of intestinal absorption. *New England J. Med.*, 255: 594, 1956.
27. McKenna, R. D., Bourne, R. H. and Matzko, A. The use of I^{131} labelled fat in the study of fat digestion and absorption in normal individuals and in patients with diseases of fat absorption. *Gastroenterology*, 32: 17, 1957.
28. Duffy, B. J., Jr. and Turner, D. A. The differential diagnosis of intestinal malabsorption with I^{131} fat and fatty acid. *Ann. Int. Med.*, 48: 1, 1958.
29. Thannhauser, S. J. and Stanley, M. M. Serum fat curves following oral administration of I^{131} labelled neutral fat to normal subjects and those with idiopathic hyperlipemia. *Tr. A. Am. Physicians*, 62: 245, 1949.
30. Stanley, M. M. and Thannhauser, S. J. The absorption and disposition of orally administered I^{131} labelled neutral fat in man. *J. Lab. & Clin. Med.*, 34: 1634, 1949.
31. Likoff, W., Berkowitz, D., Woldow, A. and Jacobs, G. Radioactive fat absorption pattern—significance in coronary artery atherosclerosis. *Circulation*, 16: 908, 1957.
32. Dublin, L. I. and Marks, H. H. Mortality among insured overweights in recent years. New York, 1952. Recording & Statistical Corp.
33. Walker, W. J. Relationship of adiposity to serum cholesterol and lipoprotein levels and their modification by dietary means. *Ann. Int. Med.*, 39: 705, 1953.
34. Abell, L. L., Levy, B. B., Brodie, B. B. and Kendall, F. E. A simplified method for the estimation of total cholesterol in serum and demonstration of its specificity. *J. Biol. Chem.*, 195: 357, 1952.
35. Youngburg, G. E. and Youngburg, M. V. Phosphorus metabolism. I. A system of blood phosphorus analysis. *J. Lab. & Clin. Med.*, 16: 158, 1930.
36. Gibson, J. G., Jr. and Evans, W. A., Jr. Clinical studies of blood volume; relation of plasma and total blood volume to venous pressure, blood velocity rate, physical measurements, age and sex in

90 normal humans. *J. Clin. Invest.*, 16: 317, 1937.

37. Gregersen, M. I. and Nickerson, J. L. Relation of blood volume and cardiac output to body type. *J. Appl. Physiol.*, 3: 329, 1950.
38. Inkley, S. R., Brooks, L. and Krieger, H. Study of methods for prediction of plasma volume. *J. Lab. & Clin. Med.*, 45: 841, 1955.
39. Beals, R. L., Reemtsma, K. and Barker, H. G. Tissue distribution of orally administered I^{131} labelled neutral fat in dogs. *Fed. Proc.*, 17: 12, 1958.
40. Van Handel, E. and Zilversmit, D. B. Validity of using I^{131} fatty acid for study of tissue distribution and incorporation into phosphatides. *Fed. Proc.*, 17: 166, 1958.
41. Kruger, F. A., Cornwall, D. G., Hamwi, G. J. and Brown, J. B. Iodinated triolein: a lipid tracer for the study of plasma lipoprotein metabolism. *Fed. Proc.*, 17: 258, 1958.
42. Turner, D. A. A simplified procedure for studying fat absorption and utilization using I^{131} labelled triolein or oleic acid. *Clin. Chem.*, 2: 273, 1956.
43. Bowes, A. D. and Church, C. F. Food Values of Portions Commonly Used, 7th ed. Philadelphia, 1951. College Offset Press.
44. Frazer, A. C., Schulman, J. H. and Stewart, H. C. Emulsification of fat in the intestine of the rat and its relationship to absorption. *J. Physiol.*, 103: 306, 1944.
45. Kellner, A., Cornell, J. W. and Ladd, A. T. Sustained hyperlipemia induced in rabbits by means of intravenously injected surface-active agents. *J. Exper. Med.*, 93: 373, 1951.
46. Korn, E. D. Lipoprotein lipase. In: Chemistry of Lipids as Related to Atherosclerosis. Springfield, Ill., 1957. Charles C Thomas.
47. Perera, G. A. The effect of significant weight change on the predicted plasma volume. *J. Clin. Invest.*, 25: 401, 1946.
48. Zilversmit, D. B. The turnover of plasma lipids. In: Chemistry of Lipids as Related to Atherosclerosis. Springfield, Ill., 1957. Charles C Thomas.
49. Berson, S. A. Pathways of iodine metabolism. *Am. J. Med.*, 20: 653, 1956.
50. Fredrickson, D. S., McCollester, D., Havel, R. and Ono, K. The early steps in the transport and metabolism of exogenous triglycerides and cholesterol. In: Chemistry of Lipids as Related to Atherosclerosis. Springfield, Ill., 1957. Charles C Thomas.
51. Zilversmit, D. B. Current concepts of lipid metabolism. *Am. J. Med.*, 23: 120, 1957.

Blood Volume in Patients with Acute Glomerulonephritis As Determined by Radioactive Chromium Tagged Red Cells*

SEYMOUR EISENBERG, M.D.
WITH THE TECHNICAL ASSISTANCE OF MARY SUE MCCALL AND SUE KELLER
Dallas, Texas

THE question of whether or not the blood volume is altered in persons with acute glomerulonephritis has never been satisfactorily resolved. Numerous studies have been reported, but these have yielded conflicting and confusing results. Brown and Rowntree [*1*], Darrow [*2*] and Waterfield [*3*] found decreased values for total blood volume in patients with "nephritis." On the other hand, Gibson and Harris [*4*], Lindy, Lundsgaard, Van Slyke and Stillman [*5*], and Hartwick and May [*6*] were unable to confirm these findings, their studies yielding essentially normal values. More recently, Cardoza [*7*] and Roscoe [*8*] have indicated that the total blood volume is expanded in persons with acute glomerulonephritis.

These reports are subject to two major criticisms. The chief defect, particularly in the earlier studies, was the failure accurately to classify the various types of renal disease; thus it is apparent that many patients with the nephrotic syndrome or chronic glomerulonephritis were included as instances of "nephritis." The more recent reports may be challenged on the grounds that the dye methods employed to estimate blood volume yield values which are falsely high because of penetration of the reference material into the extravascular space.

The present study was undertaken with the purpose of avoiding these two objections. The ten patients comprising this report had classical poststreptococcal acute glomerulonephritis; the initial measurements were made during the edematous phase of the illness, and these results were compared with the values obtained following apparent recovery. Radiochromium tagged red cells, the volume of distribution of which includes only the intravascular space, were employed as a reference from which the red cell mass was measured and plasma and total blood volumes were estimated. Two persons were studied utilizing simultaneous tagged red cell and T-1824 methods.

MATERIALS AND METHODS

Ten patients with acute glomerulonephritis were studied during the edematous phase of their illness and again after apparent recovery. In every instance the diagnosis was made on the basis of the classic clinical configuration of edema, hypertension, albuminuria, hematuria, and a history of a recent sore throat. The diagnosis was confirmed by a rise in antistreptolysin-O titer and, in two instances in which it was examined, by identification of antibodies against known nephritogenic streptococci. In nine of the ten patients the venous pressure was significantly elevated; the circulation time was slightly prolonged in three instances, normal or rapid in the remainder. Nine of the ten patients apparently recovered completely after a relatively brief illness. Patient J. C. had significant nitrogen retention and anemia for six months but ultimately improved; however, microscopic hematuria is still present thirteen months after the onset of his illness. The salient clinical features in these ten patients are presented in Table 1.

Total blood volume was determined by the radiochromium tagged red cell technic of Sterling and Gray [*9*] as modified in our laboratory. Details of the procedure were presented in a previous publication [*10*]; the method has been altered so that only 30 μc. of $Na_2Cr^{51}O_4$ were used to tag the red cells. Hematocrits were determined in triplicate using Wintrobe tubes and a centrifuge having a radius of 15 cm. from the spindle center to the bottom of the hematocrit tube. No correction factors were applied. In two patients the red cell mass was determined with radiochromium

* From the Medical Service and Radioisotope Unit of the Veterans Administration Hospital, and the Department of Internal Medicine, University of Texas Southwestern Medical School, Dallas, Texas.

TABLE I

CLINICAL DATA IN TEN PATIENTS WITH ACUTE GLOMERULONEPHRITIS

Patient	Age (yr.)	Weight Loss (kg.)	Edema-Free Weight (kg.)	V.P.* (cm. H_2O)	C.T.* (sec.)	Maximum Blood Pressure (mm. Hg)	Cardiac Enlargement*	Maximum Antistreptolysin O Titer	Maximum Blood Urea N (mg. %)	Type
F. S.	32	7	66	25	24	140/90	+	1250	25	..
S. S.	25	14	62	17	11	180/120	+	166	28	..
C. B.	32	8	77	14	10	180/115	+	250	8	..
R. M.	22	11	65	22	18	160/108	+	625	28	..
B. F.	43	12	59	25	25	180/110	+	1250	22	..
M. F.	35	10	56	17	13	170/110	+	2500	24	..
J. C.	35	11	47	27	18	140/100	−	500	80	12
W. C.	36	12	66	12	14	146/90	+	500	22	..
R. S.	50	11	73	29	17	200/110	++	1250	23	..
L. T.	38	10	72	17	27	180/100	++	1250	28	12

NOTE: V.P. = Venous pressure.
C.T. = Circulation time—decholin, arm to tongue.
Slight increases in cardiac size were detected by comparison of 6-foot chest roentgenograms before and after recovery.
Edema-free weight = the stable weight attained after loss of edema fluid.
* Values obtained at time of admission.

TABLE II

VALUES FOR TOTAL BLOOD VOLUME, RED CELL MASS AND PLASMA VOLUME IN TEN PATIENTS WITH ACUTE GLOMERULONEPHRITIS

Patient	B.V.[1] (ml./kg.)	B.V.[2] (ml./kg.)	Difference (ml./kg.)	R.C.M.[1] (ml./kg.)	R.C.M.[2] (ml./kg.)	Difference (ml./kg.)	P.V.[1] (ml./kg.)	P.V.[2] (ml./kg.)	Difference (ml./kg.)	Hematocrit[1] (%)	Hematocrit[2] (%)	Difference (%)
F. S.	90	68	−22	34	32	−2	56	36	−20	38	47	+9
S. S.	85	61	−24	34	28	−6	51	33	−18	40	45	+5
C. B.	74	60	−14	31	29	−2	44	32	−12	41	48	+7
R. M.	75	63	−12	26	24	−2	50	39	−11	34	38	+4
B. F.	77	62	−15	26	25	−1	51	38	−13	34	40	+6
M. F.	79	61	−18	25	25	0	54	36	−18	32	41	+9
J. C.	85	74	−11	27	31	+4	58	43	−15	32	41	+9
R. S.	71	66	−5	24*	22*	−2	47	44	−3	33	34	+1
W. C.	70	50	−20	25	20	−5	45	30	−15	35	40	+5
	(79)	(63)	(−16)	(28)	(26)	(+2)	(51)	(37)	(−14)	(35)	(41)	(+6)
	....	....	(1.99)	....	....	(.96)	....	....	(1.7)	....	....	(.91)
	....	....	(<.001)	....	....	(>.4)	....	....	(<.001)	....	....	(<.001)
L. T.	53	49	−4	23	21	−2	30	28	−2	44†	43	−1

NOTE: B.V.[1], R.C.M.[1], and P.V.[1] = Blood volume, red cell mass, and plasma volume at time of admission.
B.V.[2], R.C.M.[2], and P.V.[2] = Blood volume, red cell mass, and plasma volume after recovery.
Figures in parentheses represent: First line = mean.
Second line = standard error.
Third line = value.
* Patient R. S. was known to be anemic prior to the development of acute nephritis.
† Patient L. T. was not studied until after a diuresis of 6 kg.; however, a hematocrit obtained prior to the onset of diuresis was 35 per cent.

and the plasma volume with T-1824 dye [*11*]. All values presented as ml./kg. were calculated on the basis of the ultimate edema-free weight. Patient L. T. was not studied until after he had lost 6 kg. of edema fluid; the data in this patient, therefore, are presented separately.

The labeled red cell method accurately measures circulating red cell mass; from this value and the venous hematocrit, total blood volume and plasma volume may be calculated. The validity of this method has been discussed in previous reports from this laboratory [*10,12*].

RESULTS

The results of the blood volume measurements are presented in Table II. The data have been analyzed according to the method of paired observations.

Total blood volume was significantly increased ($p < .001$) during the edematous phase of the nephritic process. The mean value for blood volume in these nine subjects was 79 ml./kg. during the acute phase and 63 ml./kg. following recovery. There was, therefore, a 25 per cent increase in blood volume, which returned to normal following diuresis.

During the acute phase of the illness the plasma volume was significantly increased ($p < .001$). The mean value for plasma volume at the time of the initial observation was 51 ml./kg., whereas the mean value following treatment was 37 ml./kg. This represented a 34 per cent increase in plasma volume when the patients were edematous.

The initial mean value for red cell mass was 28 ml./kg. and the value in the same persons following recovery was 26 ml./kg. There was, therefore, no significant alteration in circulating red cell mass with the acute illness, nor was there a change during the recovery period. In one instance, patient J. C., the red cell mass decreased profoundly during a six-month period of azotemia; however, the patient ultimately improved, whereupon the red cell mass returned to normal.

The hematocrit values, on the other hand, were significantly and consistently decreased during the acute phase. The mean initial value was 36 per cent as compared with 41 per cent following recovery. These changes are consistent with the observed alterations in plasma volume against the background of a constant red cell mass. Although patient L. T. was not studied until after he had lost 6 kg. of edema fluid, a hematocrit value of 35 per cent was obtained on the day of admission to the hospital; following complete recovery the hematocrit rose to 44 per cent, indicating similar changes in plasma volume in this subject.

In two persons the plasma volume was determined with T-1824 dye. The results in these two instances are presented in Table III, together with the values derived from the red cell mass and venous hematocrit. It is apparent that the plasma volume is found to be expanded by either method and that the dye method usually yields somewhat greater values.

TABLE III
VALUES IN TWO SUBJECTS UTILIZING RADIOCHROMIUM LABELED RED CELLS AND T-1824 DYE

Patient	Values Obtained with Combined $Na_2Cr^{51}O_4$ and T-1824 Methods			Values Obtained with $Na_2Cr^{51}O_4$ Alone		
	B.V. (ml.)	R.C.M. (ml.)	P.V. (ml.)	B.V. (ml.)	R.C.M. (ml.)	P.V. (ml.)
R. S.						
Untreated	6203	1720	4438	5180	1720	3440
Treated	4689	1600	3089	4790	1600	3190
W. C.						
Untreated	4885	1860	3025	5260	1860	3400
Treated	4367	1520	2847	3750	1520	2230

B.V. = blood volume.
R.C.M. = red cell mass.
P.V. = plasma volume.

COMMENTS

The results of this study clearly indicate that the blood volume increases significantly during the edematous phase of acute glomerulonephritis. Further, it appears that the plasma volume expands selectively, there being no alteration in circulating red cell mass. The pattern of blood volume expansion, therefore, contrasts sharply with that encountered in patients with congestive heart failure in whom there is a commensurate increase in red cell mass and plasma volume [*10*]. Following diuresis and apparent recovery, the blood volume returns to normal, again as a consequence of a primary alteration in the plasma space.

These data suggest that an abnormality of salt and water metabolism is solely responsible for the hypervolemia of acute nephritis; the magnitude of this expansion is sufficient to lead to vascular overload which may play an important role in the congestive phenomena encountered. It has been suggested by LaDue [*13*], Peters [*14*] and others [*15*] that congestive heart failure is a common complication of acute glomerulonephritis. These observers cited as evidence the occurrence of edema, venous distention, cardiac enlargement, dyspnea, and electrocardiographic abnormalities. Moreover, Gore and Saphir [*16*] reported histological alterations in the myocardium of persons succumbing to this disorder. However, as was pointed out, the pattern of blood volume expansion herein reported differs from that encountered in subjects with congestive heart failure [*10*], suggesting basic pathogenetic differences.

There is a growing body of evidence that there exists a group of disorders which closely simulate congestive heart failure but which

actually have little relationship to myocardial efficiency. Eichna and his collaborators [*17*] have suggested that the congestive phenomena exhibited by persons with "steroid heart failure," acute glomerulonephritis, beri-beri, anemia and acute renal failure do not represent true myocardial failure but are examples of "non-cardiac circulatory congestion." The features which distinguish these congestive states from cardiac decompensation are increased cardiac output, decreased A-V O_2 differences, and a failure to respond to digitalis administration. Gimbel, Riegel and Glenn [*18*] induced similar congestive phenomena in normal young men by the repeated intravenous infusion of concentrated serum albumin.

Morita [*19*] and Davies [*20*] have reported hemodynamic alterations in patients with acute glomerulonephritis which substantially support the concept that true "low output cardiac decompensation" is not a common feature of this disorder. According to the recent studies of Morita [*19*], cardiac output is significantly increased and central A-V oxygen difference is decreased rather than increased. These alterations were considered to be consistent with the concept that in subjects with acute nephritis "high output congestive heart failure" develops. The clinical findings of an increase in venous pressure together with a rapid circulation time in the ten patients comprising this report are consonant with this view.

The role of hypervolemia in the pathogenesis of the congestive phenomena reported by Eichna and others [*17*] is not clear. In the subjects studied by Gimbel, Riegel and Glenn [*18*] the plasma volume was significantly expanded. In normal persons rendered edematous by prolonged steroid administration, Albert, Smith and Eichna [*17*] were unable to demonstrate consistent expansion of the plasma space; moreover, Eichna, Farber, Berger, Rader, Smith and Albert [*21*] reported normal values for blood volume in patients with acute glomerulonephritis and lower nephron nephrosis; they concluded, therefore, that hypervolemia was an inconstant feature of "non-cardiac circulatory congestion." The magnitude of the blood volume expansion in the patients comprising the present report, however, suggests that overload of the vascular tree may have played a critical role in the causation of their congestive phenomena. Which of the terms "congestive heart failure," "high output failure" or "non-cardiac circulatory congestion" should be applied is largely a semantic consideration.

Measurements of hemoglobin concentration and packed cell volume suggested the presence of a moderate anemia in all of these patients. However, the red cell mass was found to be within the normal range in eight instances, and there was no significant change in red cell mass as the hematocrit rose following diuresis. These findings indicate that the "anemia of acute glomerulonephritis," when acute anuria is not a feature of the disorder, may frequently be a dilution phenomenon which does not represent a true reduction in the total volume of circulating red cells. This "dilution anemia" may actually have important physiological consequences. Fowler, Bloom and Ward [*22*] have recently shown that expansion of the plasma volume leads to an increase in cardiac output, whereas expansion of the intravascular volume with whole blood does not effect such an increase. They have therefore concluded that the hemodynamic alterations induced by plasma volume expansion are related to a relative "anemia" rather than to a simple increase in whole blood volume. It is conceivable that similar mechanisms play an important role in the pathogenesis of the hemodynamic changes associated with acute glomerulonephritis.

It is apparent, then, that patients with acute glomerulonephritis who exhibit edema and other congestive phenomena have significantly expanded intravascular volumes. Patients lacking these clinical features were not encountered during the course of this study. The precise role of hypervolemia in the pathogenesis of this congestive syndrome is not apparent from these data. The possibility that significant myocardial damage was present in some or all of these patients cannot be excluded, nor can the influence of significant arterial hypertension be ignored. It is likely that the congestive state associated with acute glomerulonephritis results from a constellation of hemodynamic and myocardial alterations rather than from any single abnormality.

CONCLUSIONS

1. In ten persons with acute glomerulonephritis there was a 25 per cent increase in total blood volume and a 34 per cent increase in plasma volume as compared with the non-edematous recovery phase.
2. Despite lowered hematocrit values, the red

cell mass was normal in these ten patients. This suggests that the "anemia of acute glomerulonephritis" may be a dilution phenomenon.

3. Each of these ten patients exhibited congestive phenomena. The possibility that these manifestations are intimately linked with the hypervolemic state is discussed.

REFERENCES

1. Brown, G. E. and Rowntree, L. G. Blood volume in edema of glomerular nephritis and nephrosis. *Arch. Int. Med.*, 41: 44, 1929.
2. Darrow, D. C. The blood volume in cases of nephritis with edema and low serum protein concentration. *Proc. Soc. Exper. Biol. & Med.*, 23: 740, 1926.
3. Waterfield, R. L. Changes in blood volume in patients with edema of renal origin. *J. Clin. Invest.*, 9: 589, 1931.
4. Harris, A. W. and Gibson, J. G., II. Clinical studies of the blood volume. VII. Changes in blood volume in Bright's disease with or without edema, renal insufficiency, or congestive heart failure, and in hypertension. *J. Clin. Invest.*, 18: 527, 1939.
5. Linder, G. C., Lundsgaard, C., Van Slyke, D. D. and Stillman, E. Changes in the volume of plasma and absolute amount of plasma proteins in nephritis. *J. Exper. Med.*, 39: 921, 1924.
6. Hartwick, A. and May, G. Blutmengenbestimmungen mittels der Farbstoffmethode. *Ztschr. f. d. ges. exper. Med.*, 53: 677, 1926.
7. Cardoza, E. L. Hydremia in acute nephritis. *Acta med. Scandinav.*, 125: 333, 1946.
8. Roscoe, M. H. Biochemical and haematological changes in type I and type II nephritis. *Quart J. Med.*, 19: 161, 1950.
9. Sterling, K. and Gray, S. J. Determination of circulating red cell volume in man by radioactive chromium. *J. Clin. Invest.*, 29: 1614, 1950.
10. Eisenberg, S. The effect of congestive heart failure on blood volume as determined by radioactive chromium tagged red cells. *Circulation*, 10: 902, 1954.
11. Gregersen, M. D. A practical method for the determination of blood volume with the dye T-1824: survey of present basis of dye methods and its clinical application. *J. Lab. & Clin. Med.*, 29: 1266, 1944.
12. Eisenberg, S. Blood volume in patients with Laennec's cirrhosis of the liver as determined by radioactive chromium-tagged red cells. *Am. J. Med.*, 20: 189, 1956.
13. LaDue, J. S. The role of congestive heart failure in the production of the edema of acute glomerulonephritis. *Ann. Int. Med.*, 20: 405, 1944.
14. Peters, J. P. Edema of acute nephritis. *Am. J. Med.*, 14: 448, 1953.
15. Derow, H. A. Management of acute glomerulonephritis. *New England J. Med.*, 249: 144, 1953.
16. Gore, I. and Saphir, O. Myocarditis associated with acute and subacute glomerulonephritis. *Am. Heart J.*, 36: 390, 1948.
17. Albert, R. E., Smith, W. W. and Eichna, L. W. Hemodynamic changes associated with fluid retention induced in noncardiac subjects by corticotrophin (ACTH) and cortisone; comparison with the hemodynamic changes of congestive heart failure. *Circulation*, 12: 1047, 1955.
18. Gimbel, N. S., Riegel, C. and Glenn, W. W. L. Metabolism and cardiovascular studies of prolonged intravenous administration of human serum albumin. *J. Clin. Invest.*, 29: 998, 1950.
19. Morita, Y. Hemodynamic and electrolyte studies in acute glomerulonephritis. *Clin. Res. Proc.*, 5: 206, 1957.
20. Davies, C. E. Heart failure in acute nephritis *Quart. J. Med.*, 20: 163, 1951.
21. Eichna, L. W., Farber, S. J., Berger, A. R., Rader, B., Smith, W. W. and Albert, R. E. Non-cardiac circulatory congestion simulating congestive heart failure. *Tr. A. Am. Physicians*, 67: 72, 1954.
22. Fowler, N. O., Bloom, W. L. and Ward, J. A. Hemodynamic effects of hypervolemia with and without anemia. *Circulation Res.*, 6: 163, 1958.

Hereditary Aspects of Gastric Secretory Function*

Race and ABO Blood Groups in Relationship to Acid and Pepsin Production

MAURICE L. SIEVERS, M.D.

Phoenix, Arizona

SINCE the particular race and ABO blood group of an individual are incontrovertibly of hereditary origin, the differential association of a specific condition with one of these characteristics affords some evidence that it, too, may bear a relationship to inheritance. The following report is the findings of a study which has been made of the comparative level of gastric secretory function between the Caucasian and Negro races and in persons with each of the ABO blood groups.

This type of investigation requires an evaluation of the results in a large group of subjects. Direct gastric analyses present many problems for mass testing. Indirect gastric secretory studies are much easier to perform, more acceptable to the patients and qualitatively reliable [*1,2*]. Therefore, the latter procedures have been utilized. The ability of the stomach to secrete acid has been studied by tubeless gastric analysis [*3*]. Production of gastric pepsin has been evaluated indirectly by determining plasma content of pepsinogen. About 1 per cent of the acid-proteolytic enzyme produced by the chief cells escapes into the blood and is later secreted in the urine [*4*]. The level of plasma pepsinogen has been shown to reflect accurately the changes in gastric secretory function of many disease states [*1,2,5,6*].

METHOD AND MATERIAL

Plasma pepsinogen determinations were performed in duplicate on unselected patients of the Caucasian and Negro races consecutively admitted to the St. Louis Veterans Administration Hospital. The mean value of the two tests was used to characterize each person, although the variation of the two results was seldom great, as reported previously [*1*]. The laboratory method employed in determining pepsinogen content of plasma is a modification of that devised by Mirsky [*6,7*] and has been described in a previous publication [*1*].

During a longer period of time, those patients admitted to one of the medical wards of this same hospital were also submitted to tubeless gastric analysis with an azure A cation exchange resin. The method of performing tubeless gastric analysis [*3,8*], its reliability [*1,8*], and the relation of results to plasma pepsinogen [*8*] have been reported previously. The procedure involves the oral administration of an azure A cation exchange resin after a gastric secretory stimulant. If acid is produced, the azure A is displaced by the hydrogen ions and is subsequently absorbed into the blood stream and secreted in the urine. Blue urinary color (more than 0.6 mg. of dye within two hours) affords qualitative evidence of gastric acid production. This test is useful only in delineating patients with acid-secretion from those with achlorhydria, since it is not quantitatively reliable.

In those patients with positive results no further gastric analyses were performed, since this is highly reliable evidence of ability to secrete free acid [*1,8*]. Those in whom tests were initially negative were subjected to a second resin procedure, usually with a quininium resin, in order to avoid a waiting period of seven to ten days to excrete all the azure A dye from the original procedure. In addition, gastric analysis was performed by intubation, using histamine (0.01 mg. of base/kg. of body weight) as a secretory stimulus, in as many as possible of those patients with negative resin tests.

Each person included in the study had his ABO blood group determined in this laboratory by means of typing serum. The blood specimen which was drawn from pepsinogen determination was usually

* From the National Cancer Institute (U. S. Public Health Service) and Barnes Hospital and the Washington University Medical Service of the Veterans Administration Hospital, St. Louis, Missouri.

utilized for this purpose. In order to compare the ABO blood group distribution of the study group with the general population of the area, a control was derived from consecutive donors at a large St. Louis hospital (Barnes). Only donors chosen at random were included; all professional or other donors selected because of their specific blood types were eliminated from the data. ABO blood group distribution was determined for the Caucasian and Negro races separately. Further details concerning this blood bank control is included in a previous report [*9*].

Complete clinical records for each patient were carefully studied. Those persons with renal insufficiency, as reflected by blood urea nitrogen levels above 25 mg. per 100 ml., were excluded since this causes false negative tubeless gastric analyses (by retarding excretion of the dye) and false elevation of plasma pepsinogen (due to abnormal retention) [*1,2*]. In addition, the subjects in whom an abnormality of the stomach (malignancy, gastritis, peptic ulcer or pernicious anemia) or duodenal ulcer (past or present) was diagnosed by adequate criteria were excluded from final considerations. The purpose of the latter was to restrict the study of the relationship of gastric secretory function and race and ABO blood groups to persons without any apparent basic alteration in gastric physiology.

In instances in which two or more separate plasma pepsinogen determinations were made in the same person (each being performed in duplicate), the mean result was used. When several tubeless (or tube) gastric analyses were performed in a person during the study period, all of them were considered. If any was positive, the subject was designated an acid-secretor; only if all analyses were negative was he characterized as achlorhydric.

RESULTS

Gastric Acidity. Gastric acidity and ABO blood group were determined in 458 consecutive subjects; 359 were Caucasian, ninety-nine were Negro. All but four were males. Fifty-seven were excluded because of renal insufficiency (the blood urea nitrogen was greater than 25 mg. per 100 ml.) or overt gastrointestinal disease. Thus 313 Caucasian and eighty-eight Negro patients were included in the study. Table I gives the details of the number of subjects excluded and the basis for this.

TABLE I

NUMBER OF SUBJECTS IN WHOM GASTRIC ACIDITY AND ABO BLOOD GROUP WERE DETERMINED, BY RACE, INCLUDING THOSE PATIENTS WITH AZOTEMIA, DUODENAL ULCER AND GASTRIC DISEASE

Race	Blood Group	Category of Subjects				
		Total Group	Azotemia	Duodenal Ulcer	Gastric Disease	Study Group
Caucasian	O	169	9	13	1	146
	A	149	8	7	3	131
	B	29	1	2	0	26
	AB	12	1	1	0	10
	Total	359	19	23	4	313
Negro	O	53	2	3	0	48
	A	24	2	0	1	21
	B	19	1	2	0	16
	AB	3	0	0	0	3
	Total	99	5	5	1	88
Both	O	222	11	16	1	194
	A	173	10	7	4	152
	B	48	2	4	0	42
	AB	15	1	1	0	13
	Total	458	24	28	5	401

The age distribution, by blood group and race, of the 401 study subjects in whom gastric acidity was determined is shown in Table II. The range, mean and median age of Caucasians is not significantly different for those with blood groups O, A and B; there are too few subjects with group AB to make comparison useful.

TABLE II

RANGE, MEAN AND MEDIAN AGE OF SUBJECTS IN WHOM GASTRIC ACIDITY WAS DETERMINED, BY RACE AND ABO BLOOD GROUP

Blood Group	Caucasian Race			Negro Race			Both Races		
	Range	Mean	Median	Range	Mean	Median	Range	Mean	Median
O	23–86	53.7	52	21–73	44.7	43	21–86	50.6	50
A	19–87	52.2	52	20–77	45.8	45	19–87	51.3	51
B	24–79	50.1	49	29–54	40.1	41	24–79	45.7	47
AB	45–68	61.3	58	65–79	72.0	72	45–79	64.4	62
Total	19–87	53.0	52	20–79	43.4	44	19–87	50.8	50

TABLE III

ABO BLOOD GROUP DISTRIBUTION OF 401 STUDY SUBJECTS IN WHOM GASTRIC ACIDITY WAS QUALITATIVELY DETERMINED, COMPARED WITH THAT OF 32,945 BLOOD BANK CONTROL SUBJECTS, BY RACE

Blood Group	Caucasian Race				Negro Race				Both Races		
	Study Group		Control		Study Group		Control		Study Group		Weighted Controls
	No.	%	No.	%	No.	%	No.	%	No.	%	(%)
O	146	46.6	14,918	45.3	48	54.5	713	51.1	194	48.4	46.6
A	131	41.9	13,611	41.3	21	23.9	353	25.3	152	37.9	37.7
B	26	8.3	3,248	9.9	16	18.2	269	19.3	42	10.5	12.0
AB	10	3.3	1,168	3.5	3	3.4	60	4.3	13	3.2	3.7
Total	313	100.1	32,945	100.0	88	100.0	1,395	100.0	401	100.0	100.0

Similar findings apply to the Negroes, except that subjects with group B were somewhat younger than those with group O and A. The mean age of the white patients was 9.6 years older than that for the Negroes.

In Table III, the ABO blood group distribution of the 401 subjects included in this series is compared, by race, with blood bank control subjects from the same geographical area. In both races the study groups approximate the control subject. This affords some evidence that these patients are a random sampling, representative of the general population of the area.

Eighty-seven of the 401 study subjects in whom tubeless gastric analysis and ABO blood group were evaluated were considered to be achlorhydric (sixty-eight Caucasian and nineteen Negro); and 314 were classified as acid-secretors (245 Caucasian and sixty-nine Negro). Even though the vast majority of patients were over forty years of age, the finding of achlorhydria in about 22 per cent of each race appears somewhat excessive. This is probably a result of the fact that the achlorhydric group, as delineated here, includes some hypochlorhydric subjects. It has not been possible to limit the achlorhydric group to those in whom the absence of ability to secrete free acid was confirmed by tube gastric analysis, using histamine as a secretory stimulant.

For various reasons, intubation could not be performed in some subjects with negative findings by tubeless gastric analysis. However, extensive observations in this laboratory [*10*] have shown that a single negative tubeless gastric analysis is indicative of achlorhydria (as established by intubation, with histamine, 0.01 mg. of base/kg., as the secretory stimulus) in 53 per cent of patients, while 77 per cent secrete less than 10 degrees of free acid. If a second tubeless procedure is also negative, absence of free acid is found by intubation in 72 per cent, and 90 per cent produce less than 10 degrees. A positive resin test is highly reliable evidence of the ability of the stomach to secrete acid, if the procedure is carried out correctly [*1,8,10*]. In this study, subjects were classified as acid-secretors if any resin test was positive or tube gastric analysis revealed free acid. Those with all negative tubeless tests (one or more) and/or absence of free acid on tube gastric analysis were considered achlorhydric.

The eighty-seven subjects classified as achlorhydric were selected on the basis of the following criteria:

No. of Patients	Results of Tubeless Gastric Analyses		Results of Tube Gastric Analysis
	Initial Test	Subsequent Tests	
18	Negative	Not performed	Not performed
3	Negative	Indeterminate	Not performed
14	Negative	Negative	Not performed
8	Negative	Not performed	Negative
3	Negative	Indeterminate	Negative
41	Negative	Negative	Negative

It should be noted that in forty-one of the eighty-seven "achlorhydric" patients there were negative results in all three procedures; in eleven patients results by intubation and one tubeless test were negative; in fourteen results in two tubeless procedures were negative; and, among twenty-one patients, the only basis for classification as achlorhydric was a single tubeless gastric analysis which revealed negative results. On the other 314 patients all or some of their tests were indicative of acid-secreting ability.

In Table IV the number of patients classified as secretors and non-secretors of acid is shown, by race and ABO blood group. Achlorhydria (as defined here) occurred in almost identical percentages of Caucasians (21.7 per cent) and Negroes (21.6 per cent). Since there are too few Negroes in the study group for evaluation of the acid-producing status by blood group, the two races will be considered together. Comparative observations will be confined to blood groups O and A, since these are the only ones with large numbers of patients. The percentage of both Caucasians and Negroes in whom secretion of free acid occurred is approximately the same in each of these two blood types; but both races have a higher percentage of persons with achlorhydria among those with group A (27.5 and 23.8 per cent, respectively) than those with group O (13.7 and 14.6 per cent, respectively). However, only in the Caucasian race is the difference in the frequency of achlorhydria between subjects with group O and A statistically significant ($P < 0.007$); the lack of significance for the Negro race ($P = 0.56$) may be a reflection of the limited number of observations.

Of all acid-secretors, 53.2 per cent have blood group O, while only 31 per cent of those with achlorhydria have this blood type. In contrast, patients with blood group A constitute 35.4 per cent of acid-secretors and 47.1 per cent of those patients with achlorhydria. Free acid is produced in 86.1 per cent of patients with blood group O, and in only 73 per cent of patients with blood group A. This is graphically shown in Figure 1. The difference in frequency of acid-secretion and non-acid secretion occurring in subjects of both races combined is highly significant for these two blood groups ($P < 0.004$).

Plasma Pepsinogen. Plasma pepsinogen was

TABLE IV

NUMBER AND PER CENT OF PATIENTS WITH AND WITHOUT ACID-SECRETING ABILITY, BY RACE AND ABO BLOOD GROUP

Race	Blood Group	Each Race as a Whole						Each Category	
		Acid-Secretion		Achlorhydria		Both		Acid-Secretion	Achlorhydria
		No.	%	No.	%	No.	%	%	%
Caucasian	O	126	51.4	20	29.4	146	46.6	86.3	13.7
	A	95	38.8	36	52.9	131	41.9	72.5	27.5
	B	20	8.2	6	8.8	26	8.3	76.9	23.1
	AB	4	1.6	6	8.8	10	3.3	40.0	60.0
	Total	245	100.0	68	99.9	313	100.1	78.3	21.7
Negro	O	41	59.4	7	36.8	48	54.5	85.4	14.6
	A	16	23.2	5	26.3	21	23.9	76.2	23.8
	B	9	13.0	7	36.8	16	18.2	56.3	43.7
	AB	3	4.3	0	0.0	3	3.4	100.0	0.0
	Total	69	99.9	19	99.9	88	100.0	78.4	21.6
Both	O	167	53.2	27	31.0	194	48.4	86.1	13.9
	A	111	35.4	41	47.1	152	37.9	73.0	27.0
	B	29	9.2	13	14.9	42	10.5	69.0	31.0
	AB	7	2.2	6	6.9	13	3.2	53.8	46.2
	Total	314	100.0	87	99.9	401	100.0	78.3	21.7

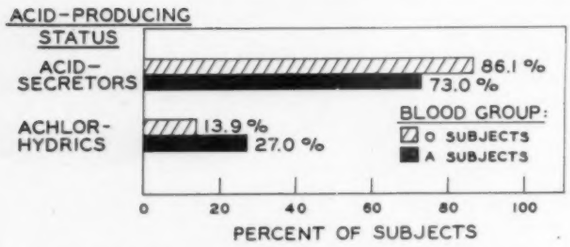


FIG. 1. Acid-producing status of subjects with blood group O and A.

determined in 732 persons, all but seven of whom were male. There were 567 Caucasians and 165 Negroes. Among those of the white race, seventy-four had gastrointestinal disease and twenty-two had azotemia. These ninety-six Caucasians were excluded from the study; in the 471 white persons who were included there were no overt factors influencing pepsinogen production or retention in the plasma. Of the 165 Negro subjects, twenty-three were excluded, as shown in Table v. Thus, 142 Negroes are utilized in the study. A total of 613 persons from both races are included from the 732 on whom tests were performed.

The age distribution of the subjects used in the study is shown in Table VI. The mean age of the Caucasians was higher (50.6 years) than that of the Negroes (43.8 years). Since comparative studies will be concerned principally with subjects with blood group O and A, it should be noted that the mean age is slightly higher for Caucasians with blood group O (52.4 years) than A (49.3 years), but slightly lower for Negroes of type O (42.3 years) than A (47.0 years). However, the mean age of the two races combined is about the same for these two blood groups (48.9 and 49.1 years, respectively).

TABLE V

NUMBER OF SUBJECTS IN WHOM PLASMA PEPSINOGEN AND ABO BLOOD GROUP WERE DETERMINED, BY RACE, INCLUDING THOSE PATIENTS WITH AZOTEMIA, DUODENAL ULCER AND GASTRIC DISEASE

Race	Blood Group	Category of Subjects				
		Toal Group	Azotemia	Duodenal Ulcer	Gastric Disease	Study Group
Caucasian	O	253	10	31	3	209
	A	235	7	19	6	203
	B	58	4	7	2	45
	AB	21	1	6	0	14
	Total	567	22	63	11	471
Negro	O	88	8	9	0	71
	A	49	0	3	1	45
	B	24	1	1	0	22
	AB	4	0	0	0	4
	Total	165	9	13	1	142
Both	O	341	18	40	3	280
	A	284	7	22	7	248
	B	82	5	8	2	67
	AB	25	1	6	0	18
	Total	732	31	76	12	613

The ABO blood group distribution of the 613 subjects included in this study is compared with blood bank control subjects, by race, in Table VII. Both Caucasians and Negroes approximate the distribution of the control subjects, with only a slight excess of patients with blood group A. Thus the group selected for this study is very similar to the general population in ABO blood group composition.

The mean plasma pepsinogen values and standard deviation from the mean is shown by ABO blood group and race in Table VIII. The mean value of plasma pepsinogen is slightly higher for Caucasians (527 units/ml.) than for Negroes (517 units/ml.). This is not statistically

TABLE VI

RANGE, MEAN AND MEDIAN AGE OF SUBJECTS IN WHOM PLASMA PEPSINOGEN WAS DETERMINED, BY RACE AND ABO BLOOD GROUP

Blood Group	Caucasian Race			Negro Race			Both Races		
	Range	Mean	Median	Range	Mean	Median	Range	Mean	Median
O	25–84	52.4	54	22–71	42.3	40	22–84	48.9	49
A	19–83	49.3	50	23–79	47.0	44	19–83	49.1	49
B	22–79	48.3	50	24–69	45.2	44	22–79	47.4	47
AB	28–73	49.6	47	26–36	32.5	35	28–73	45.9	46
Total	19–84	50.6	51	22–79	43.8	43	19–84	49.0	48

TABLE VII

ABO BLOOD GROUP DISTRIBUTION OF 613 STUDY SUBJECTS IN WHOM PLASMA PEPSINOGEN WAS DETERMINED, COMPARED WITH THAT OF BLOOD BANK CONTROL SUBJECTS, BY RACE

Blood Group	Caucasian Race			Negro Race			Both Races		
	Study Group		Control* (%)	Study Group		Control* (%)	Study Group		Weighted Control (%)
	No.	%		No.	%		No.	%	
O	209	44.4	45.3	71	50.0	51.1	280	45.7	46.7
A	203	43.1	41.3	45	31.7	25.3	248	40.5	37.6
B	45	9.6	9.9	22	15.5	19.3	67	10.9	12.1
AB	14	3.0	3.5	4	2.8	4.3	18	2.9	3.6
Total	471	100.1	100.0	142	100.0	100.0	613	100.0	100.0

* Refer to Table III for number of control subjects of each race and each ABO blood group.

significant ($P > 0.1$). There is a somewhat higher mean plasma pepsinogen value in this study than in a previous one reported from this laboratory [*14*]. A modification of method of controlling pH of the substrate was made between the two studies. The tests in this series were performed at the optimum pH (1.5) with greater uniformity; this allowed maximum proteolytic activity for pepsinogen.

Comparative statistical evaluation of the mean plasma pepsinogen values, by race and blood group, is shown in Table IX. There are no significant differences between the Negro and Caucasian races. However, both whites and Negroes have a significantly higher mean plasma pepsinogen in subjects with group O (561 and 572 units/ml., respectively) than in those with group A (501 and 458 units/ml., respectively). These differences are highly significant for the white ($P < 0.01$) and Negro races ($P < 0.01$) or for both races combined ($P < 0.01$). In the Negro race the lower value for persons with group B (493 units/ml.) than those with group O is also significant ($P < 0.01$). Although the difference between Caucasian with group B and O is in the same direction, it is of a lesser degree which is not statistically significant ($P > 0.05$). However, for the two races combined, the greater value for subjects with group O than B is significant ($P > 0.01$). In comparison with group O mean results, the white persons with group AB have a lower value (426 units/ml.) of significance ($P < 0.01$); the Negro subjects have no significant difference for these two groups ($P > 0.05$); but for the two races combined a significant difference exists ($P < 0.05$). There are no statistically significant differences in mean plasma pepsinogen values for Negroes and Caucasians (separately or combined) between the individuals with blood group A, B and AB.

TABLE VIII

MEAN PLASMA PEPSINOGEN AND STANDARD DEVIATION FROM MEAN, BY RACE AND ABO BLOOD GROUP

Race	Group	No. of Patients	Plasma Pepsinogen (units/ml.)		
			Range	Mean	S.D.*
Caucasian	O	209	102–1416	561	229.0
	A	203	17–1605	501	226.9
	B	45	85–1223	521	233.1
	AB	14	189– 695	426	158.8
	Total	471	17–1605	527	228.4
Negro	O	71	267–1368	572	207.2
	A	45	130– 966	458	198.5
	B	22	199– 926	439	179.0
	AB	4	303– 787	628	225.0
	Total	142	130–1368	517	208.4
Both	O	280	102–1416	564	223.0
	A	248	17–1605	494	222.5
	B	67	85–1223	494	219.0
	AB	18	189– 787	470	189.1
	Total	613	17–1605	524	223.8

* Standard deviation.

The distribution of plasma pepsinogen values is shown for patients with blood group O and A,

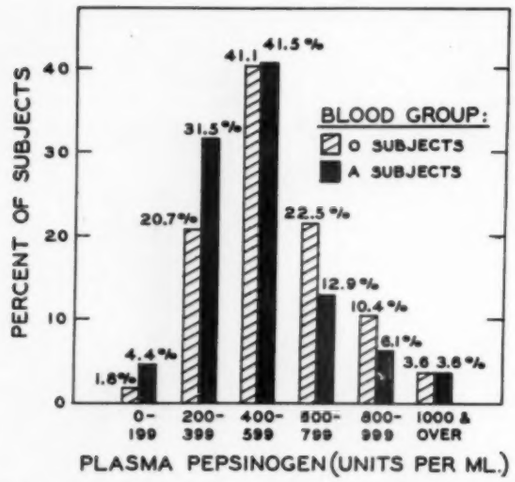


FIG. 2. Comparative distribution of plasma pepsinogen results in subjects with blood group O and A.

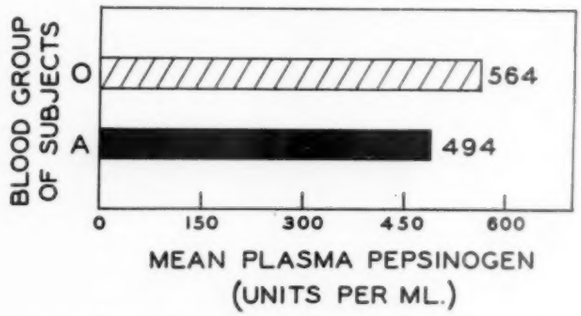


FIG. 3. Mean plasma pepsinogen values in subjects with blood group O and A.

by race, in Table x. Both races have higher percentages of subjects with group A than O with the lower pepsinogen values; the reverse is true for the higher ones. This is graphically illustrated in Figure 2. It is noted that in 22.5 per cent of the subjects with group O there are plasma pepsinogen values of less than 400 units/ml., while in 35.9 per cent of the subjects with group A they are below this value. On the other hand, results greater than 600 units/ml. were encountered in 36.5 per cent of the patients with group O, but in only 22.6 per cent of those with group A.

In Figure 3, the mean plasma pepsinogen results of patients with blood group O and A are compared. As noted previously, the 70 units/ml. excess for the mean value of the former is highly significant.

COMMENTS

The evidence presented in this study is strong support for a relationship between the ABO blood groups and the status of acid and pepsin

TABLE IX

STATISTICAL EVALUATION OF DIFFERENCES BETWEEN PLASMA PEPSINOGEN VALUES, BY RACE AND BLOOD GROUPS

"t" VALUES*

(FOR DIFFERENCES BETWEEN BLOOD GROUPS, FOR EACH RACE)

Race	O:A	O:B	O:AB	A:B	A:AB	B:AB	O:Other 3	A:Other 3	B:Other 3	AB:Other 3
Caucasian..	2.63	1.04	2.98	0.51	1.67	1.74	2.84	2.14	0.06	2.40
Negro.....	2.98	2.95	0.49	0.39	1.47	1.60	0.33	2.37	2.17	1.00
Both.....	3.62	2.33	2.06	0.001	0.12	0.14	1.25	2.87	1.22	1.23

"t" VALUES *

(FOR DIFFERENCES BETWEEN RACES FOR EACH BLOOD GROUP)

	O:O	A:A	B:B	AB:AB	All
Caucasian:Negro	0.40	1.31	1.60	1.75	0.51

* "t" values may be converted to "P" as follows:

"t"	"P"
<1.96	>0.05
1.96 to 2.57	<0.05 to >0.01
2.58 or more	<0.01

TABLE X

DISTRIBUTION OF PLASMA PEPSINOGEN VALUES IN SUBJECTS WITH BLOOD GROUP O AND A, BY RACE

Plasma Pepsinogen (units/ml.)	Caucasian Race				Negro Race				Both Races			
	O		A		O		A		O		A	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
0–99	0	0.0	2	1.0	0	0.0	0	0.0	0	0.0	2	0.8
100–199	5	2.4	6	3.0	0	0.0	3	6.7	5	1.8	9	3.6
200–299	15	7.2	22	10.8	6	8.5	6	13.3	21	7.5	28	11.3
300–399	30	14.4	41	20.2	7	9.9	9	20.0	37	13.2	50	20.2
400–499	45	21.5	42	20.7	15	21.1	11	24.4	60	21.4	53	21.4
500–599	41	19.6	40	19.7	14	19.7	10	22.2	55	19.6	50	20.2
600–699	23	11.0	20	9.8	13	18.3	2	4.4	36	12.9	22	8.9
700–799	21	10.1	10	4.9	6	8.5	0	0.0	27	9.6	10	4.0
800–899	12	5.7	7	3.5	6	8.5	1	2.2	18	6.4	8	3.2
900–999	9	4.3	4	2.0	2	2.8	3	6.7	11	3.9	7	2.8
1000 and over	8	3.8	9	4.4	2	2.8	0	0.0	10	3.6	9	3.6
Total	209	100.0	203	100.0	71	100.1	45	99.9	280	99.9	248	100.0

production by the stomach. Similar findings have been noted in this laboratory in respect to intrinsic factor production [*11*], as measured by indirect means (Schilling test [*12*]). Thus, a higher percentage of subjects with blood group O than A retain good gastric secretory function in all three of these parameters. It is implied from this that gastric atrophy has some inherited basis which is reflected more often in association with blood group A. No significant racial variation in gastric secretory function was found between Caucasians and Negroes in the present study.

If these observations and implications are considered further, some of the distorted ABO blood group distributions found among those with certain gastrointestinal diseases [*9,13–22*] may be explained. For example, the excessive frequency of blood group O found in patients with duodenal ulcer [*14,16,18*] may relate to the fact that this is a condition dependent on the preservation of gastric secretory function. If secretory failure develops less often in subjects with blood group O than in those with group A, duodenal ulcer would be expected to occur more frequently in the former subjects regardless of whether acid and pepsin are involved in an etiologic or permissive role.

Gastric malignancy and pernicious anemia both occur in relationship with decreased gastric secretory function. In patients with cancer of the stomach, achlorhydria [*23*] and decreased pepsin production [*1,2,5*] are much more frequent than in others of the same sex, race and age group. Virtually all patients with the adult type of Addisonian pernicious anemia have achylia (no acid, pepsin or intrinsic factor production). In either of these conditions there is an excess of blood group A over control subjects [*9,13,16,18,21,22*]. It is possible that the association of these two conditions with blood group A is merely a reflection of the fact that their occurrence is related to gastric secretory failure (atrophy) which also occurs more frequently in those with blood group A than O.

It is uncertain that the altered gastric secretory function plays a direct etiological role for either gastric cancer or duodenal ulcer. However, it does seem apparent that pernicious anemia is a direct result of gastric atrophy with lack of production of intrinsic factor (which is almost invariably accompanied by anacidity and absent pepsin) so that extrinsic factor (vitamin B_{12}) fails to be absorbed.

In essence, then, in persons with blood group O there is an increased tendency for a condition associated with elevated acid and pepsin production to develop, while in persons with blood group A there is a greater likelihood of conditions developing associated with decreased or

absent acid and pepsin elaboration. Køster et al. [*15*] have made a further interesting observation in this regard. They noted that, among 413 patients with gastric cancer, blood group A occurred more often in those with achlorhydria than in those in whom the ability to secrete acid was retained (although both groups exceeded the control subjects in frequency of blood group A). On the other hand, the patients with gastric cancer who still secreted free acid had group O blood type significantly more often than those with achlorhydria.

Mosbech and Videbaek [*24*] have suggested that achlorhydria may be related to inherited factors. Achlorhydria may also reflect an underlying influence to an increased incidence of pernicious anemia or gastric malignancy. All three of these conditions presumably have a more or less important relationship to gastric atrophy. On this basis, it might be expected that blood group A would be represented excessively among patients with gastric atrophy —even without any overt gastrointestinal disease—as selected on the basis of achlorhydria and/or low or absent pepsin production.

It is possible that the apparently greater tendency of gastric atrophy to develop in persons with blood group A than in those with blood group O may not be a simple, direct hereditary influence. But at this time the listing of indirect pathways for such an event would be highly speculative.

SUMMARY

The production of gastric acid and pepsin in Caucasians and Negroes has been studied by indirect tests in relation to the ABO blood groups. In general, secretory function was about the same for the two races. However, in both the whites and Negroes, impairment of gastric secretion was more frequent in subjects with blood group A than in those with group O. Free acid was produced by 86.1 per cent of patients with blood group O, while only 73.0 per cent of those with blood group A did so. The mean value of plasma pepsinogen was higher for subjects with blood group O (564 units/ml.) than in those with group A (494 units/ml.).

The evidence suggests that functional gastric atrophy occurs more often in subjects with blood group A than in those with group O and may be related to inherited factors. It is also suggested that the associations which have been noted between certain diseases and ABO blood groups (i.e., pernicious anemia and gastric malignancy with an excess of blood group A; and duodenal ulcer with an excess of blood group O) may actually relate primarily to the altered gastric secretory function which seems to serve at least a permissive role in all of these conditions.

Acknowledgment: I wish to express my gratitude to Dr. Benno K. Milmore, Epidemiologist, and Mr. J. William Lloyd, Statistician, (both from the National Cancer Institute, U. S. Public Health Service) for their advice and statistical analyses.

REFERENCES

1. Sievers, M. L. and Fischer, G. L. Indirect gastric secretory studies: a comparison of tubeless gastric analysis and plasma pepsinogen determination as screening procedures. *Am. J. Digest. Dis., N. S.*, 2: 363, 1957.
2. Spiro, H. M., Ryan, A. D. and Jones, C. M. The relation of blood pepsin to gastric secretion with particular reference to anacidity and achylia. *Gastroenterology*, 30: 563, 1956.
3. Segal, H. L., Miller, L. L. and Plumb, E. J. Tubeless gastric analysis with an azure A ion exchange compound. *Gastroenterology*, 28: 402, 1955.
4. Janowitz, H. D. and Hollander, F. Relation of uropepsinogen excretion to gastric pepsin secretion in man. *J. Appl. Physiol.*, 4: 53, 1951.
5. Hoar, C. S. and Browning, J. R. Plasma pepsinogen in peptic-ulcer disease and other gastric disorders. *New England J. Med.*, 255: 153, 1956.
6. Mirsky, I. A., Futterman, P. and Kaplan, S. Blood plasma pepsinogen. II. Activity of plasma from "normal" subjects, patients with duodenal ulcer and patients with pernicious anemia. *J. Lab. & Clin. Med.*, 40: 188, 1952.
7. Mirsky, I. A., Futterman, P., Kaplan, S. and Broh-Kahn, R. H. Blood plasma pepsinogen. I. Source, properties and assay of proteolytic activity of plasma at acid reactions. *J. Lab. & Clin. Med.*, 40: 17, 1952.
8. Sievers, M. L. and Gieselman, R. V. Tubeless gastric analysis: evaluation of a technic using a dye-resin compound. *Am. J. Digest. Dis., N. S.*, 1: 241, 1956.
9. Sievers, M. L. Some factors in occurrence and prognosis of gastric malignancy. II. ABO blood groups. To be published.
10. Sievers, M. L. Unpublished observations, 1958.
11. Sievers, M. L. and Gallagher, N. I. Unpublished observations, 1958.
12. Schilling, R. F. Intrinsic factor studies. II. The effect of gastric juice on the urinary excretion of radioactivity after the oral administration of radioactive vitamin B_{12}. *J. Lab. & Clin. Med.*, 42: 860, 1953.
13. Aird, I., Bentall, H. H. and Fraser Roberts, J. A. A relationship between cancer of the stomach and the ABO blood groups. *Brit. M. J.*, 1: 799, 1953.
14. Aird, I., Bentall, H. H., Mehigan, J. A. and Fraser Roberts, J. A. Blood groups in relation to

peptic ulceration and carcinoma of colon, rectum, breast and bronchus. *Brit. M. J.*, 2: 315, 1954.

15. Køster, K. H., Sindrup, E. and Steele, V. ABO blood groups and gastric acidity. *Lancet*, 2: 52, 1955.
16. Buckwalter, J. A., Wohlwend, E. B., Colter, D. C., Tidrick, R. T. and Knowler, L. A. ABO blood groups and disease. *J. A. M. A.*, 162: 1210, 1956.
17. Billington, B. P. Gastric cancer: relationship between ABO blood groups, site and epidemiology. *Lancet*, 2: 859, 1956.
18. Buckwalter, J. A., Turner, J. H., Raterman, L., Tidrick, R. T. and Knowler, L. A. Ethnologic aspects of the ABO blood groups disease association. *J. A. M. A.*, 165: 327, 1957.
19. Hogg, L., Jr. and Pack, G. T. The controversial relationship between blood group A and gastric cancer. *Gastroenterology*, 32: 797, 1957.
20. Balme, R. H. and Jennings, D. Gastric ulcer and the ABO blood-groups. *Lancet*, 1: 1219, 1957.
21. Cregor, W. P. and Sortor, A. T. Incidence of blood group A in pernicious anemia. *Arch. Int. Med.*, 98: 136, 1956.
22. A collective series from a number of centers, an association between blood group A and pernicious anemia. *Brit. M. J.*, 2: 723, 1956.
23. Hitchcock, C. R., MacLean, L. D. and Sullivan, W. A. The secretory and clinical aspects of achlorhydria and gastric atrophy as precursors of gastric cancer. *J. Nat. Cancer Inst.*, 18: 795, 1957.
24. Mosbech, J. and Videbaek, A. Mortality from and risk of gastric carcinoma among patients with pernicious anemia. *Brit. M. J.*, 2: 390, 1950.

Review

Anatomy of Body Water and Electrolytes*

I. S. EDELMAN, M.D. *and* J. LEIBMAN, M.D.
San Francisco, California

RECENT studies, principally involving the application of tracer technics to problems in the field of body water and electrolyte metabolism, make it timely to review and redefine anatomical concepts [*1,2*]. Definitions of the anatomical organization of body fluids are by no means a trivial exercise since they critically influence the interpretations of such varied studies as metabolic balances, tracer dilution measurements and tissue analyses. The purpose of this review is to re-examine and to some extent revise prevailing concepts of the body content and distribution of water, sodium, potassium and chloride in man.

Ideas about body fluid and electrolyte anatomy have changed greatly in the last three decades. These ideas have been influenced by the limitations of the technics of study, as well as the nature of the particular problem under consideration. Chemical analyses of tissues and body fluids led to proposals concerning the organization of the body fluids [*3*]. The early demonstration by histological technics of membrane envelopes encasing cell fluid gave the impression that body fluids could be adequately described in two phases, intracellular and extracellular. This distinction is justified by the fundamental differences in electrolyte structure of these two phases [*3–7*]. Furthermore, cellular activity and survival depend on the maintenance of the characteristic electrolyte patterns of both the intracellular and extracellular fluids [*5*]. By extrapolation from tissue analyses to the whole organism, this original hypothesis was amplified so that water and electrolyte structure has been described in terms of three compartments, i.e., plasma, interstitial and intracellular [*5,8*]. This scheme, if accurate, would make it possible to define intracellular composition from observations on the composition of plasma and a suitable method for measuring total extracellular fluid volume and total body constituents [*7*]. The accuracy of this stratagem is based on the approximate identity of the electrolyte composition of plasma and interstitial fluid. The evidence for such a similarity in composition, which is quite convincing, has been summarized previously [*9,10*]. One of the most promising technical advances in the study of fluid and electrolyte anatomy was the introduction of tracers to measure total body water and total exchangeable electrolytes [*1*]. These technics were designed to provide *in vivo* estimates of total quantities of water and electrolytes as a basis for the clearer understanding of their differential distribution and physiological functions.

The prospect of defining abnormalities of sodium, potassium, chloride and water distribution across cell membranes *in vivo* in man inspired a considerable search for a substance suitable for measuring total extracellular fluid [*1,11–19*]. The evidence that chloride is almost exclusively extracellular in skeletal muscle led to its use as a measure of extracellular volume [*4–6,12*]. Analogous anions, including bromide, thiocyanate, thiosulfate, sulfate and ferrocyanide, both stable and isotopic forms, were also used for this purpose [*13–17*]. The saccharides mannitol, sucrose and inulin, were introduced for the measurement of extracellular fluid volume to circumvent the objection of permeability of cells to ions [*14,18,19*]. There were two assumptions in these studies: (1) extracellular fluid existed in a homogeneous state and therefore was measurable by the volume of dilution of a single substance, and (2) pathological changes would not affect the homogeneity of this phase. There is now abundant evidence to show that the first and more important of these assumptions is erroneous [*2,20–29*].

The heterogeneity of the extracellular phase has become apparent from studies on bone

* From the Department of Medicine, University of California School of Medicine, San Francisco, California.

[*20–22*], dense connective tissue [*23,24*], and gastrointestinal contents [*25–29*]. Before these studies were reported there appeared to be irreconcilable differences in intracellular electrolyte contents and concentrations based on tissue analyses compared with *in vivo* multiple tracer dilution measurements [*30–32*]. The average total intracellular electrolyte concentrations derived from tracer dilution studies were about 115 mEq./L. of potassium, 35 mEq./L. of sodium and 25 mEq./L. of chloride, while from tissue analyses these figures were approximately 150 mEq./L. of potassium, 8 mEq./L. of sodium and 1 to 2 mEq./L. of chloride [*5,6,8*]. The former estimates were based on the presumed identity of the sucrose and inulin volumes of dilution with the volume of total extracellular fluid. This assumption has been shown to be in error, since it assigns excess bone sodium, perhaps some bone chloride and water, some of the extracellular phase of dense connective tissues, probably much of the extracellular water and ions of cartilage, and most if not all of the water and electrolytes of transcellular fluid to the intracellular phase [*2,20–29,33*]. The precise definition of the composition of all the extracellular phases, both fluid and solid, cannot as yet be made. First order estimates, however, are feasible and will be included in the sections to follow.

A separate description of the organization of body water, sodium, potassium and chloride is given because electrolyte anatomy is not coextensive with water content, i.e., the supporting framework of the body contains ions independent of water content.

TABLE 1
TOTAL BODY WATER IN NORMAL MAN

Reference No.	Method*	Total Body Water (% of body weight)			
		Children			
		0–1 mo.	1–12 mo.	1–10 yr.	
45, 48–49	D_2O + AP	75.7 (n = 20)†	64.5 (n = 15)	61.7 (n = 24)	
		Males			
		10–16 yr.	17–39 yr.	40–59 yr.	60+ yr.
37, 45, 48	D_2O	59.0 (n = 9)	60.4 (n = 39)	55.4 (n = 8)	54.1 (n=3)
41, 42	SG	.....	61.4 (n = 106)	55.3 (n = 78)	.....
31, 41, 50	AP	58.5 (n = 2)	59.9 (n = 96)	54.3 (n = 28)	51.0 (n = 17)
43	HTO	.....	57.5 (n = 7)	51.8 (n = 13)	.....
Mean (all methods)		58.9 (n = 11)	60.6 (n = 248)	54.7 (n = 127)	51.5 (n = 20)
		Females			
		10–16 yr.	17–39 yr.	40–59 yr.	60+ yr.
37, 45 48, 49	D_2O	57.3 (n = 7)	51.4 (n = 19)	46.9 (n = 5)	46.2 (n = 5)
42	SG	.....	53.8 (n = 23)	46.9 (n = 29)	.....
31, 50	AP	.....	44.6 (n = 19)	44.6 (n = 4)	45.1 (n = 9)
Mean (all methods)		57.3 (n = 7)	50.2 (n = 61)	46.7 (n = 38)	45.5 (n = 14)

* D_2O = deuterium oxide.
AP = antipyrine and its derivatives.
SG = specific gravity.
HTO = tritium oxide.
† n = number of subjects.

WATER CONTENT AND DISTRIBUTION

The first estimates of body water content in man were obtained late in the nineteenth century by desiccation of cadavers [*34–36*]. Indirect methods of measuring body water have been successfully applied to human subjects [*1,2*]. Dilution of deuterium oxide, tritium oxide, antipyrine and its derivative, n-acetyl 4-aminopyrine, and the specific gravity technic have been shown to be reasonably accurate measures of body water content in normal animals and in normal man [*37–50*]. The suitability of deuterium oxide and tritium oxide for such measurements has been confirmed by comparisons with desiccation and tissue-sampling studies [*38,39,43*]. There is good agreement in body water estimates in normal man by simultaneous measurements with deuterium oxide and antipyrine [*44,45*], antipyrine and specific gravity [*41,46*], tritium oxide and antipyrine [*43*] and deuterium oxide and tritium oxide [*47*]. Although the rates of molecular exchange of water between blood, interstitial fluid and cell water vary widely from tissue to tissue, no regions of non-exchangeable water are known to exist [*38*].

The available data on body water measured *in vivo* by dilution methods in man are summarized in Table 1. These data confirm the trends outlined previously [*42,48,49*]. While there is considerable individual variation, body water content tends to decrease progressively with age. A detailed analysis of the relationships between body water and age, body weight, height and

TABLE II
PLASMA VOLUME IN NORMAL ADULT MAN BY T-1824 DILUTION

Reference No.	Sex	ml./kg. of Body Weight		
		17–39 yr.	40–59 yr.	60+ yr.
59–61	Males	45.2 (n = 69)*	43.5 (n = 22)	47.6 (n = 3)
59–61	Females	43.8 (n = 76)	37.2 (n = 9)	.....

* n = number of subjects.

surface area has been published previously [*49*]. A significant difference in mean body water content exists between males and females, which appears at puberty and persists throughout the life span. The evidence indicates that the statistical differences in body water content expressed as a fraction of body weight in adults with respect to age and sex are primarily a consequence of differences in body fat content [*42*]. During the first year of life, however, there is decreasing hydration because of diminution in plasma-interstitial fluid content [*49*].

As more detailed information has appeared, concepts of the organization of body water have become more complex. Basic to these concepts is the attempt to distinguish clearly between intracellular and extracellular phases. The delineation of the former is based on the recognition of clearly defined cellular boundaries and a characteristic electrolyte pattern consisting predominantly of potassium, magnesium, phosphate and protein [*5,51*]. Future studies will probably demonstrate subdivisions of intracellular water and electrolytes based either on differences in composition of cellular components (i.e., cytoplasm, microsomes, mitochondria, nuclei) or on differences in composition of cells of various organs and tissues. The concept of a single intracellular phase is still useful in describing the organization of the whole organism, however. The extracellular phase, both aqueous and solid components, must be subdivided to interpret properly the data derived from dilution, metabolic balance or tissue analysis. Attempts to characterize the total extracellular phase by the volume of dilution of a single tracer have led to confusion of anatomical with "physiological" quantities. The heterogeneity of the extracellular structures makes it unlikely that any dilution method will be suitable for accurate definition of all the non-intracellular water and electrolytes. Indeed, the conflicting estimates of extracellular fluid provided by volume of dilution of different tracers led to the conclusion that "not only are size estimates unreliable but the very nature of the extracellular phase is obscure" [*10*]. It is proposed that the extracellular water and electrolytes may be described with reasonable accuracy as consisting of four main subdivisions: (1) plasma, (2) interstitial and lymph fluid, (3) dense connective tissue, cartilage and bone, and (4) transcellular fluids.

Plasma Volume. The boundaries of the plasma volume are provided by the cellular elements of blood and the heart and blood vessels. The anatomic boundaries are not sharply restrictive since plasma proteins and cellular elements cross into and out of the circulation in the liver, spleen and bone marrow. Nevertheless, the anatomic and functional significance of the plasma and blood volume has been clearly and extensively justified in a number of reviews [*52–54*]. The methods for estimating plasma volume fall into two categories: (1) albumin or globulin labeling by dye (T-1824), I^{131} or antigens, and (2) red cell labeling with isotopes or carbon monoxide [*52–60*]. Plasma volume estimated by protein tagging averages 10 to 15 per cent higher than estimates based on red cell dilution and venous hematocrit [*55,56*]. These differences have been analyzed in terms of the loss of tagged protein during the mixing phase, the errors in hematocrit measurements because of trapped plasma and true differences between small vessel and large vessel hematocrits [*54,57*]. The evidence indicating minimal loss of labeled protein during the mixing phase has been summarized, and estimates of plasma volume by these methods may be accepted as reasonably accurate [*52,57,58*].

Representative T-1824 volumes of dilution are presented in Table II. Although these average estimates of plasma volume may be inexact, it is unlikely that "true" plasma volume differs by more than 5 per cent from these figures [*52,57*]. The values in males tend to exceed those in females, but the overlap between these groups is considerable. In any one series the range of values for plasma volume varies from 34 to 58 ml. per kg. of body weight and comprises about 7.5 per cent of body water. Little information is presently available on the differences in plasma

TABLE III
VOLUME OF DISTRIBUTION OF SACCHARIDES IN NORMAL MAN

Reference No.	Sex	Saccharide	Equilibration Time (hr.)	ml./kg. of Body Weight	
				Mean	Range
63	M (n = 7)*	Mannitol	6	159	141–187
63	M (n = 7)	Inulin	6	157	136–175
64	M (n = 11)	Sucrose	5	175	140–197

* n = number of subjects.

volume with age and sex referred to body weight and surface area.

Interstitial-Lymph Fluid Volume. The plasma and interstitial-lymph fluid compartments are in close functional and structural relationship [*62*]. The similarities and differences in chemical composition of these fluids have been evaluated previously [*10*]. In spite of an extensive literature on these phases precise estimates of the total volumes of interstitial and lymph fluid have not been achieved. The use of dilution methods *in vivo* for such estimates has been difficult to interpret because of the structural complexities and dissimilarities in rates of equilibration in muscle, skin and connective tissue [*23,24*]. No substance is yet available which is excluded from cells and which is distributed rapidly in all the interstitial-lymph fluid. Dense connective tissues differ from the rapidly equilibrating tissues, in that 75 per cent of their extracellular phase apparently equilibrates slowly with the saccharides [*23*]. Exclusive of 75 per cent of such tissues, the saccharides may provide a reasonable measure of the volume of interstitial-lymph fluid. Table III summarizes some of the available data on such estimates in man. After a correction is made for plasma volume, the rapidly equilibrating interstitial-lymph volume may be estimated as 120 ml. per kg. of body weight or 20 per cent of total body water in normal young adult males. This quantity includes the rapidly equilibrating phase of dense connective tissue [*23*]. No assessment has been made of the variable relationships between interstitial-lymph volume and body weight or surface area which may exist for each age and sex group.

TABLE IV
WATER CONTENT OF BONE, CARTILAGE, TENDON AND SKIN IN ADULT MAN

Reference No.	Tissue	ml./kg. of Tissue	% of Body Water	Remarks
66	Bone	340 (n = 37)*	...	.....
67	Bone	284 (n = 2)	8.5	Total skeleton including marrow taken shortly after death
21	Bone	318 (n = 16)	...	Tissue aliquots excluding marrow taken shortly after death
68	Cartilage	705	...	Tissue aliquots taken postmortem
69	Cartilage (dog)	750 (n = 13)	...	Tissue aliquots taken from normal animals
70	Tendon (rabbit)	618 (n = 14)	...	Tissue aliquots taken from normal animals
23	Tendon (dog)	667 (n = 8)	...	Tissue aliquots taken from normal animals
71	Skin	623 (n = 25)	...	Tissue aliquots taken postmortem

* n = number of subjects.

Dense Connective Tissue, Cartilage and Bone Water. Bone, cartilage and dense connective tissues have unique chemical structures. In addition, differences in anatomic structure, as well as sparseness of vascularity, differentiate these tissues from those in which tracers equilibrate more rapidly [*10,21–24*]. The solid phase of bone has a dispersed microcrystalline structure which acts as a surface for ionic exchange, thereby binding sodium in quantities far in excess of its concentration in interstitial fluid [*21,22,65*]. For these reasons the structural tissues are designated as a distinct subdivision of body water.

Table IV summarizes some of the available data on water content of the structural tissues in man. Bone is obviously quite dry, but its bulk accounts for its sizable contribution to total body water, i.e., about 8.5 per cent [*21,67*]. Direct measurements of the total quantity of water in cartilage and dense connective tissues have not yet been reported. However, an estimation can be derived from available data on collagen distribution in the guinea pig, if the collagen contents of guinea pig and man are assumed to be comparable. A calculation based on the presumption first that 70 per cent of tendon and cartilage is water, and second, that the measured water content of tendon is characteristic of dense connective tissues indicates that the total osseous-free connective tissue water in a man weighing 70 kg. amounts to approximately 4.2 L. [*72*]. Since 25 per cent of this quantity is penetrated rapidly by the saccharides, and is therefore

TABLE V
TRANSCELLULAR FLUID VOLUME IN MAN

Reference No.	Source	ml./kg. of Body Weight	% of Body Water	Remarks
29	Intraluminal gastrointestinal	7.4	1.4	Obtained at postmortem examination
25	Intraluminal gastrointestinal (dog)	19.0	3.0	Normal dogs sacrificed after twenty-four-hour fast
78	Cerebrospinal fluid	2.8	...	.....
	Biliary tree	2.1	...	Calculated from the average gallbladder volume (50 ml.) and 5 per cent of total liver water
	Remainder	3.0	...	Calculated as 15 per cent of organ weights, including the mucosal layer of the gastrointestinal tract plus aqueous and vitreous humor

presumably part of the free interstitial-lymph fluid, there remains 3.2 L. of unpenetrated extracellular dense connective tissue water (including cartilage but not bone) [*23*]. This represents 45 ml. per kg. of body weight and 7.5 per cent of total body water. The relatively acellular character of both bone and dense connective tissue is confirmed both histologically and by the finding that the chloride concentration per kg. of tissue water is similar to the plasma concentration [*10,23*]. Hence, the water of dense connective tissue and bone may be considered almost entirely extracellular.

A reasonable estimate of total skeletal water is 3.4 L. for a normal man weighing 70 kg., based on bone being 16 per cent of body weight [*21,34,67*]. From present knowledge of bone structure it is unlikely that more than 10 per cent of this quantity is accessible to penetration by the saccharide tracers, since most of the water of bone is bound water although it is exchangeable [*21,73*]. Inaccessible extracellular bone water, therefore, approximates 45 ml. per kg. of body weight or 7.5 per cent of total body water.

Transcellular Fluids. The term transcellular fluid was introduced to designate a variety of extracellular fluid collections which are not simple transudates and which have the common property of being formed by the transport activity of cells [*2*]. These fluids are found in the salivary glands, the pancreas, the liver and biliary tree, the thyroid gland, the gonads, the skin, the mucous membranes of the respiratory and gastrointestinal tracts, and the kidneys, in addition to the cavitary fluids of the eye, the cerebrospinal fluid and the intraluminal fluid of the gastrointestinal tract. Electrolyte composition of these fluids differs from that of a simple ultrafiltrate of plasma, and the saccharides, as well as other extracellular fluid tracers, do not appear in bile, gastrointestinal secretions or cerebrospinal fluid [*14,19,74–77*].

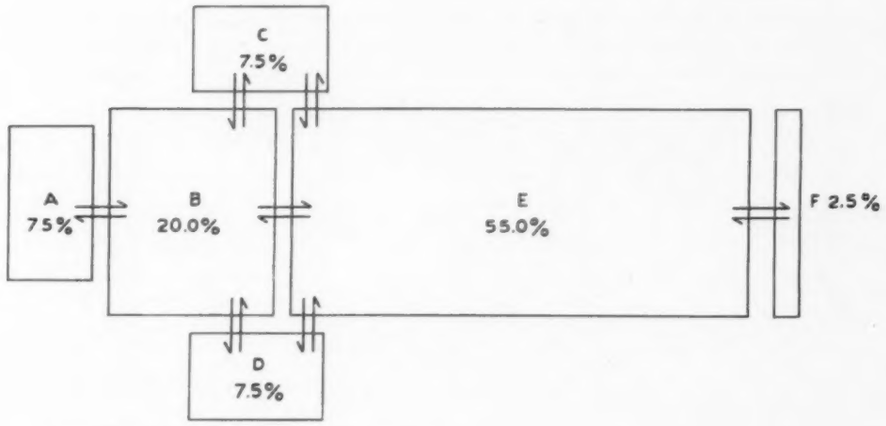
Table V lists estimated transcellular fluid volumes in man and, for comparison, the intraluminal gastrointestinal water content of the dog. The figures on intraluminal gastrointestinal water, the largest subdivision of transcellular water, can only be accepted as tentative in man since agonal or postmortem shifts of water and electrolytes might have induced systematic errors. The calculation of the remainder, based on estimated normal weights of kidneys, thyroid, pancreas, gonads, salivary glands, and the fractional contributions of mucous and secretory glands of the respiratory and gastrointestinal tracts, the sweat glands and the eyes, may be in error by a factor of 2 or 3, but in absolute terms it is reasonable to assume that these components of transcellular fluid are no less than 100 ml. or more than 600 ml. in the average adult. The estimated total transcellular fluid volume, therefore, is 15.3 ml. per kg. of body weight, or 2.5 per cent of total body water.

SUMMARY OF BODY WATER DISTRIBUTION

Body water anatomy in the normal population cannot be precisely characterized because of significant individual variations in body water content with age, sex and weight. Furthermore,

TABLE VI
BODY WATER DISTRIBUTION IN AN "AVERAGE" NORMAL YOUNG ADULT MALE

Source	ml./kg. of Body Weight	% of Total Body Water
Plasma	45	7.5
Interstitial-lymph	120	20.0
Dense connective tissue and cartilage	45	7.5
Inaccessible bone water	45	7.5
Transcellular	15	2.5
Total extracellular	270	45.0
Total body water (D_2O)	600	100.0
Total intracellular	330	55.0



A. PLASMA WATER–7.5% OF BODY WATER
B. INTERSTITIAL–LYMPH WATER–20.0%
C. DENSE CONNECTIVE TISSUE AND CARTILAGE WATER–7.5%
D. BONE WATER–7.5%
E. INTRACELLULAR WATER–55.0%
F. TRANSCELLULAR WATER–2.5%

FIG. 1. Schematic diagram of body water distribution in a normal young adult man.

the relative amounts of plasma, interstitial fluid and transcellular fluid may vary considerably in the individual. However, a simplified schema is possible, which is outlined in Table VI and depicted in Figure 1. These calculations emphasize both the heterogeneity of the extracellular fluids and the considerable magnitude of those extracellular fluids which are not a direct part of the plasma interstitial-lymph pool. In disease states translocations of fluid and electrolytes among these subdivisions may be of vital significance. For example, in patients with obstruction of the lower part of the bowel, the total transcellular fluid content may double or treble at the expense of other extracellular fluid subdivisions. Experimental data must also be evaluated in the light of striking species differences in the proportions of body water and electrolytes in these compartments [*25–29*]. This is exemplified by the finding that the gastrointestinal water content in rabbits is tenfold that found postmortem in man [*29*].

SODIUM CONTENT AND DISTRIBUTION

The *in vivo* measurement of body sodium content in man by radioisotope dilution is complicated by the existence of a sizable pool of slowly exchangeable or non-exchangeable bone sodium [*21,79,80*]. Inasmuch as bone contains 35 to 40 per cent of total body sodium, the exchangeable sodium pool is substantially less than the total body quantity [*67*]. On the other hand, all the non-osseous sodium apparently achieves exchange equilibrium with radiosodium in about twenty-four hours. It has been repeatedly demonstrated that the ratio of tissue to serum specific activities, including gastrointestinal fluid and transudates, approaches unity in both dog and man after twenty-four hours of radiosodium equilibration, and that serial serum specific activity changes little after this time [*26,79–83*]. The average increase of exchangeable sodium pool size is about 1 per cent per day after the first twenty-four hours, which is adequately explained by slow penetration into bone [*83*]. Unfortunately, little data from postmortem studies of man are available for comparison with dilution values. The earlier figures on total body sodium content in cadavers are unreliable because of technical defects [*84*] or because the subjects were not free of chronic serious disease [*85*]. Recent whole body analyses on two subjects not chronically ill have been reported, and these data are listed in Table VII. The nonexchangeable bone fraction was calculated in order to relate the whole body value to total exchangeable sodium. The mineral phase of bone consists of crystals, with an hydroxyapatite structure, which lie in the ground substance, forming a periodic pattern around the collagen fibers. A significant amount of exchangeable sodium is adsorbed on the surface of these crystals [*21,86*]. Therefore, bone sodium may be regarded as existing in three phases: (1) free extracellular fluid sodium, (2) exchangeable sodium adsorbed to the surface of bone crystals,

TABLE VII

ESTIMATION OF TOTAL EXCHANGEABLE SODIUM FROM TOTAL BODY SODIUM CONTENT IN MAN*

Total Body Sodium		Total Skeletal Sodium (mEq.)	Calculated Non-Exchangeable Sodium† (mEq.)	Calculated Total Exchangeable Sodium‡		Ratio of Total Exchangeable Sodium to Total Body Sodium§
mEq.	mEq./kg. of Body Weight			mEq.	mEq./kg. of Body Weight	
3,575	67.6	1,554	1,088	2,487	47.0	0.70
4,161	57.1	1,455	1,019	3,142	43.1	0.76

* Taken from Forbes and Lewis [*67*].
† 0.7 × total skeletal sodium.
‡ Total body sodium minus calculated non-exchangeable sodium.
§ Assuming radiosodium exchange equilibrium in all tissues other than bone.

(3) non-exchangeable sodium in the crystalline phase. In man the ratio of the twenty-four-hour bone sodium to serum sodium specific activity varies from 0.18 to 0.38 [*21,79,80,83,87*]. The average non-exchangeable bone sodium fraction, therefore, is about 0.7, which is somewhat greater than the value found in the dog [*21*]. The calculated values of total exchangeable sodium in the two subjects listed in Table VII are well within the normal range based on twenty-four-hour Na^{24} dilution.

The available data on total exchangeable sodium in normal adults are listed in Table VIII. These are mean values, and there is a striking absence of any trend with either sex or age. Individual variations are of some magnitude since most authors reported a range of about 32 to 49 mEq. per kg. of body weight. In the newborn, exchangeable sodium content was 86 ± 6.0 mEq. per kg. of body weight, differing significantly from the values obtained in adults [*88*]. This finding is in accord with the high total body water content in the newborn and in infants [*49*].

TABLE VIII

TOTAL EXCHANGEABLE SODIUM IN NORMAL ADULTS

Reference No.	mEq./kg. of Body Weight		
Male			
31, 79–81, 89–96	18–33 yr.	34–50 yr.	51–70 yr.
	41.4 (n = 78)	41.4 (n = 22)	40.1 (n = 19)
Female			
79–81, 89, 91–93, 95–98	16–33 yr.	35–72 yr.	
	39.2 (n = 31)	41.4 (n = 22)	

From the data and calculations in Tables VII and VIII it appears that exchangeable sodium is about 70 per cent of total body sodium and that the average total body sodium content of the normal adult is about 58 mEq. per kg. of body weight. From the data on extracellular fluid volumes and sodium concentration, the intracellular quantity has been estimated and compared with values derived from histochemical figures.

Plasma Sodium. The mean plasma sodium concentration in normal fasting well hydrated subjects in this laboratory was 144.8 ± 2.5 mEq. per L. (eighteen subjects, eleven males and seven females; age range, twenty-four to thirty-nine years). This value agrees with the published normal range [*99,100*]. The plasma sodium pool, as derived from the mean plasma volume and the plasma sodium concentration, averages 6.5 mEq. per kg. of body weight. The range of normal values will be quite large, of course, since there inevitably will be a conjunction of either low or high concentrations and volumes in certain subjects. The absolute quantity of plasma sodium will be as low as 230 mEq. in a small

TABLE IX

SODIUM, POTASSIUM, AND CHLORIDE CONCENTRATION IN PLASMA, TRANSUDATES, AND LYMPH IN ADULT MAN

	mEq./L. (unpublished data [*100*])	Transudate/Serum* [*10,132*]	Lymph/Serum† [*106,107*]
Serum sodium	144.8 ± 2.5 (n = 18)‡	0.95 ± 0.02 (n = 39)	1.00 ± 0.01 (n = 5)
Serum potassium	4.58 (n = 18)	0.92 ± 0.06 (n = 22)	0.95 ± 0.01 (n = 5)
Plasma chloride	100.2 ± 2.4 (adult males) 102.3 ± 2.9 (adult females) (n = 167)	1.03§ (n = 29)	1.02 (man) (n = 5) 1.05 (dog) (n = 8)

* Each component was measured as mEq./kg. water in patients with liver, heart and kidney diseases and in normal students.

† Each component was measured as mEq./L. in patients with leukemia or metastatic malignancy. The lymph protein content in these samples averaged 70 per cent of the plasma value.

‡ n = number of subjects.

§ Transudate protein concentration <1 gm./100 ml.

woman and as much as 750 mEq. in a big man. The average quantity of plasma sodium, however, represents 15.9 per cent of total exchangeable sodium, or 11.2 per cent of total body sodium. The former is the more meaningful figure since the non-exchangeable bone sodium is probably excluded from the compensatory reactions which occur in acute sodium depletion or in metabolic acidosis [*22,101–103*]. In the rat, non-exchangeable bone sodium is not subject to removal until bone resorption occurs [*104*].

Interstitial-Lymph Sodium. Transudate sodium concentration differs from serum sodium concentration by about 5 per cent which is in accord with the Gibbs-Donnan prediction [*10,105*]. Characteristic values for serum, transudate and lymph sodium concentrations or ratios are listed in Table IX. The actual interstitial or lymph fluid sodium concentration will vary, depending mainly on the differences in the protein content of these fluids from that of plasma. The application of a Gibbs-Donnan correction factor of 0.97 yields an estimated sodium concentration of 140.4 ± 2.5 mEq. per L. for both interstitial fluid and lymph. Therefore this phase, which has a mean volume of 120 ml. per kg. of body weight, contains an average of 16.8 mEq. of sodium per kg. of body weight. Hence, in normal healthy young adults, 41 per cent of the total exchangeable sodium, or 29 per cent of the total body sodium, is in the interstitial fluid-lymph phase. Both the absolute and relative amounts will vary considerably among subjects, since there is a normal distribution of values of sodium concentration and of interstitial-lymph volume. The combined plasma-interstitial-lymph fluids contain about 57 per cent of the total exchangeable sodium or 40 per cent of total body sodium; this has special functional significance, since it was found that these fluids contribute 70 per cent of the sodium lost during acute sodium depletion in dogs [*103*].

Dense Connective Tissue, Cartilage and Bone Sodium. These tissues are composed of tightly packed collagen bundles lying in an interfibrillary cement with few cells and few blood vessels. Cartilage has almost no blood vessels, but in some instances has fairly numerous columns of cells, whereas bone is distinguished by its mineral structure

As can be seen in Table X the sodium concentration of dense connective tissues tends to be slightly higher than the normal interstitial fluid sodium concentration, while cartilage and bone contain considerably more sodium than can be accounted for by the interstitial fluid concentration of sodium in these tissues. Manery [*10*] summarized the evidence indicating that cartilage sodium is completely exchangeable with radiosodium, that the "excess" sodium is bound to organic constituents of the matrix, and that chondroitin sulfate is the major cation binding constituent. The values for bone sodium concentration and bone sodium in excess of chloride

TABLE X

SODIUM CONTENT OF DENSE CONNECTIVE TISSUE, CARTILAGE AND BONE

Reference No.	Tissue	Sodium (mEq./kg.)		Chloride (mEq./kg.)		Excess Sodium* (mEq./kg.)
		FFD Tissue†	Tissue Water	FFD Tissue	Tissue Water	FFD Tissue
109	Skin—connective tissue phase (man, n = 14)‡	76.1	154.5	63.7	129.7	.....
23	Tendon (dog, n = 8)	293.7	146.5	258.0	128.8	.....
69	Cartilage (dog, n = 13)	905.5	293.8	220.8	71.6	600.6
67	Total skeleton (man, n = 2)	309.5	523.0	69.7	117.0	223.3

* Sodium in excess of the amount associated with chloride, which is assumed to be extracellular *in toto*. The factor employed was (145 × 0.95/105 × 1.05).

† Concentration expressed in mEq./kg. fat-free dry solids.

‡ n = number of subjects.

listed in Table x are 10 to 30 per cent higher than those reported previously on bone samples in man [*21*], but agree well with those obtained by an isotope technic [*108*].

The slow penetration of saccharides into tendon indicates that 75 per cent of the extracellular water of dense connective tissues is excluded from the free interstitial pool [*23,24*]. If these tissues contain an average of 150 mEq. of sodium per kg. of dense connective tissue water, uniformly distributed, then the sodium content of the slowly equilibrating phase can be calculated. A reasonable estimate based on the calculated water content of this phase would be 6.8 mEq. per kg. of body weight, or 16.5 per cent of total exchangeable sodium or 11.7 per cent of total body sodium.

TABLE XI

PARTITION OF BONE SODIUM IN MAN

	mEq./kg. of Body Weight	% of Total Bone Sodium
Interstitial fluid sodium*	3.8	15
Rapidly exchangeable bone sodium (24 hours)†	7.5	30
Slowly exchangeable bone sodium (1 to 7 days)	2.7	10
Non-exchangeable bone sodium	14.8	60
Total bone sodium	25.0	100

* Marrow-free bone [*21*]. This would be a maximum estimate based on the chloride content of bone.

† Includes free interstitial fluid sodium.

The major fraction of cartilage and bone sodium resides in bone, since cartilage constitutes a very small fraction of body weight. The calculated indirect estimate of total bone sodium of 23 mEq. per kg. of body weight [*21*] compares favorably with the direct determinations on two human cadavers, which yielded values of 20.0 and 29.4 mEq. per kg. [*67*]. If bone chloride is taken as a measure of the free interstitial phase, then about 85 per cent of bone sodium is excluded from this phase. In addition to the interstitial and rapidly exchanging crystalline phases of approximately 2.7 mEq. of sodium per kg. of body weight, there is also a slowly exchanging bone sodium phase [*83*]. Table XI gives estimates of the partition of sodium in bone based on an average value of 25 mEq. of bone sodium per kg. of body weight. The combined bone and cartilage rapidly exchangeable sodium pool, including both crystalline and free interstitial phases, is about 8.0 mEq. per kg. of body weight, or 19.5 per cent of total exchangeable sodium or 13.8 per cent of total body sodium. If the penetration of extracellular tracers into bone does not exceed the value found in tendon, then 3.8 per cent or less of total bone sodium is in the free interstitial phase.

Transcellular Fluid Sodium. The sodium content and concentration of these heterogeneous fluids varies tremendously. The exact quantities of these fluids are not known, but approximate

TABLE XII
SODIUM, POTASSIUM AND CHLORIDE CONCENTRATIONS IN TRANSCELLULAR FLUIDS

Reference No.	Fluid	Sodium (mEq./L.)	Potassium (mEq./L.)	Chloride (mEq./L.)
112	Saliva	33.1 ± 13.4	19.5 ± 3.4	33.9 ± 10.2
113	Gastric juice	60.4 (9–116)	9.2 (0.5–32.5)	84.0 (7.8–154.5)
113	Ileal fluid	129.4 (105.4–143.7)	11.2 (5.9–29.3)	116.2 (90–136.4)
113	Cecal fluid	52.5	7.9	42.5
113	Pancreatic juice	141.1 (113–153)	4.6 (2.6–7.4)	76.6 (54.1–95.2)
113	Bile	148.9 (131–164)	4.98 (2.6–12)	100.6 (89–117.6)
78	Cerebrospinal fluid	140.0 (130–150)	3.3 (2.7–3.9)	126.8 (115.5–132.4)
114	Aqueous humor (rabbits)	143.0 (141.7–145.0)	4.7	107.9 (106.2–109.5)
115	Sweat	45.0 (18–97)	4.5 (1–15)	57.5 (18–97)

NOTE: Figures in parentheses indicate range.

TABLE XIII
BODY SODIUM DISTRIBUTION IN AN "AVERAGE" NORMAL YOUNG ADULT MALE

	mEq./kg. of Body Weight	% of Total Exchangeable Sodium	% of Total Body Sodium
Plasma	6.5	15.9	11.2
Interstitial-lymph	16.8	41.0	29.0
Dense connective tissue and cartilage	6.8	16.5	11.7
Exchangeable bone	8.0	19.5	13.8
Total bone	25.0	.....	43.1
Transcellular	1.5	3.7	2.6
Total exchangeable extracellular	39.6	96.6	68.3
Total extracellular	56.6	.....	97.6
Total body sodium	58.0	142.9	100.0
Total intracellular	1.4	3.4	2.4

estimates of water content have been given in the first section. Table XII lists some characteristic sodium concentrations of transcellular fluids. The wide variations in concentration indicate that these fluids generally are not in simple diffusion equilibrium with plasma. Although radiosodium exchanges completely with the sodium in the transcellular fluids in which it has been measured (gastrointestinal fluid, pancreatic juice and cerebrospinal fluid) [*26,110,111*], the saccharides penetrate slowly or not at all [*14,19,74–77*].

The major component of these fluids is the intraluminal sodium of the gastrointestinal tract. Postmortem studies in man indicate that the gut contains 0.3 to 1.3 mEq. of sodium per kg. of body weight. The next largest transcellular pool, the cerebrospinal fluid, contains approximately 0.4 mEq. per kg. of body weight based on the average volumes and concentrations given in Tables V and XII. Similarly, the remaining transcellular fluids contain an additional 0.6 mEq. per kg. of body weight. The total transcellular sodium is, therefore, approximately 1.5 mEq. per kg. of body weight or 3.7 per cent of total exchangeable sodium or 2.6 per cent of total body sodium.

SUMMARY OF DISTRIBUTION OF SODIUM IN MAN

Table XIII and Figure 2 summarize the data on sodium distribution presented in the previous sections. The difference between total body sodium and the calculated total extracellular sodium has been assigned to the intracellular phase. The calculated average intracellular sodium concentration based on this method of anatomic dissection, therefore, is 1.4 mEq. per kg. of body weight, or 4.2 mEq. per L. of cell water. This value compares favorably with most of the reported histochemical estimates [*116–118*]. (see Table XXI.) Values described for the normal state are subject to great change with disease. Edema formation involves 20 to 100 per cent increases in total exchangeable sodium in patients with liver, kidney or heart disease [*119*]. Acute depletion of up to 20 per cent of body sodium may occur prior to death, a process which involves plasma and interstitial fluid sodium primarily [*103*]. Addison's disease may be associated with depletion of 50 per cent of total exchangeable sodium [*120*]. Under such pathophysiological circumstances gross distortions of the anatomic relations for sodium among the phases outlined will occur.

POTASSIUM CONTENT AND DISTRIBUTION

Cadaver analyses provided the original quantitation of body potassium content, and these data have recently been confirmed [*67,84,85*]. The values derived from such studies have been remarkably constant, and as with measurements of other mineral components of the body, were significantly affected by body fat content. Radiopotassium has furnished a technic of measuring total exchangeable body potassium [*121*]. Potassium^{42} has been generally employed for these determinations; whole body radioactivity resulting from naturally occurring potassium^{40} has also been utilized [*122*]. Results obtained with

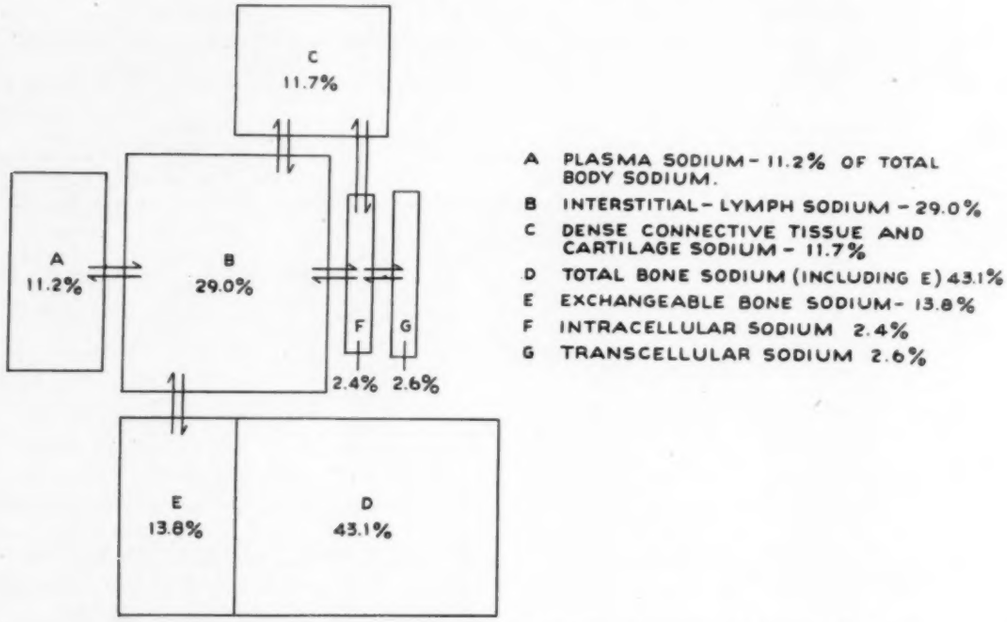


FIG. 2. Schematic diagram of body sodium distribution in a normal young adult man.

these *in vivo* technics have correlated fairly well with the cadaver data, implying that in contrast to radiosodium, there is relatively complete mixing of radiopotassium with body potassium during an equilibration period of forty hours. The total exchangeable potassium measured with potassium[42] comprised 75 to 93 per cent (mean of 85 per cent) of body potassium when compared with whole body counting of potassium[40] [*122*]. Data derived from rabbit studies had previously indicated that the exchangeable potassium constituted 95 per cent of the body potassium [*121,123*]. The total exchangeable potassium is undoubtedly made up of many components; the various intracellular compartments must have multiple exchange rates, and this is easily demonstrated by serial changes in specific activity in various tissues [*124*]. The slowly equilibrating tissues consist primarily of red blood cells, brain and bone [*121,124*]. No data are available on direct measurements of non-exchangeable potassium; however, calculations from the cadaver data [*67*] reveal differences in body potassium content compared to the values derived by potassium[42] dilution. When potassium content is referred to total body water and the cadaver data is compared to K^{42} data in subjects from a roughly similar age group, a 15 per cent difference is apparent, which is quite similar to the mean difference noted in the comparison between potassium[40] and potassium[42] estimations [*122*]. Table XIV compares

TABLE XIV

A COMPARISON OF TOTAL EXCHANGEABLE POTASSIUM (FORTY-HOUR POTASSIUM[42] DILUTION) WITH TOTAL BODY POTASSIUM

Method	Total Body Potassium		Total Exchangeable Potassium		% of Total Body Potassium
	mEq./kg. of Body Weight	mEq./kg. of Body Water	mEq./kg. of Body Weight	mEq./kg. of Body Water	
Chemical—cadaver analysis [*67*]	51.5	95.3	44.9*	82.0	85
Potassium[40] dilution [*122*]	54.6	....	48.9	....	90
Chemical—rabbits [*121*]	58.6	....	56.1	....	95

* Table XV, males, aged thirty-four to fifty years.

exchangeable potassium with total body potassium estimated by potassium[40] whole body counting in man, by cadaver analysis in man and by direct whole body analyses in rabbits. These data indicate that potassium[42] dilution at forty to forty-eight hours measures from 85 to 95 per cent of total body potassium. About 3 per cent of this difference may be ascribed to the potassium of red blood cells, which is only about two-thirds equilibrated with potassium[42] at the end of forty hours [*27,121*].

The available data on body potassium measured *in vivo* by dilution of potassium[42] are summarized in Table xv. These data confirm the obvious differences in relative body content of muscle and fat which exist between the sexes and the various age levels; relative muscle content is highest in young males and decreases with age, whereas relative fat content is highest in older females. Total body water should be a more constant standard of reference than body weight, and the data in Table xv suggest that the difference in potassium content between the various age and sex categories may be less when exchangeable body potassium is referred to total body water. Remarkably little change in exchangeable potassium per kg. of body weight takes place up to adulthood, in contrast to sodium content, which at birth is high and then declines rapidly. The potassium content in infants and children is about the same as that in young adults [*125*]. The diminution of both absolute and relative exchangeable potassium in later years may perhaps be explained best by an increase in relative fat content, associated with a decrease in lean body mass [*126*]. The relationships between potassium content and age, body weight, height, and surface area have been described previously [*121,126*]. As might be expected from our knowledge of the distribution of potassium, a significantly higher correlation has been noted between total exchangeable potassium and lean body mass as derived from total body water data [*127,128*].

Plasma Potassium. Although physiologically crucial, the total plasma potassium content is quite small. The normal plasma potassium concentration is 4.58 mEq. per L. in fasting young adult males (sixteen subjects) in this laboratory, which is close to the published normal range [*99,100*]. The plasma potassium pool averages 0.2 mEq. per kg. of body weight; in view of this low content, the total quantity of plasma potassium will range only from 7 mEq. in a small woman to 21 mEq. in a large man. Obviously, the plasma potassium is a minute fraction of the total body potassium, comprising a maximum of 0.4 per cent of body potassium.

TABLE XV
TOTAL EXCHANGEABLE POTASSIUM IN NORMAL ADULTS

Reference No.	mEq./kg. of Body Weight		
Male			
	18–33 yr.	34–50 yr.	51–75 yr.
31, 94, 95, 121, 122, 126, 127, 129, 130	48.9 (n=73)*	44.9 (n=13)	39.1 (n=18)
Female			
	16–33 yr.	34–81 yr.	
95, 98, 126, 127, 129–131	37.3 (n=72)	30.9 (n=30)	
Reference No.	mEq./L. of Total Body Water		
Male			
	18–33 yr.	34–50 yr.	
31, 121, 127, 129, 130	80.4 (n=32)	82.0 (n=10)	
Female			
	16–33 yr.	34–81 yr.	
127, 129, 130	75.3 (n=26)	62.8 (n=6)	

* n = number of subjects.

Interstitial Fluid-Lymph Potassium. Earlier reports had indicated inexplicably marked differences between serum and transudate potassium concentrations [*10*]. However, more recent data comparing serum with ultrafiltrates and with edema, pleural and ascitic fluid [*105,132*] have been much more consistent with the small theoretical differences expected from the Gibbs-Donnan effect. (Table ix.) The estimated potas-

TABLE XVI
POTASSIUM CONTENT OF DENSE CONNECTIVE TISSUE, CARTILAGE AND BONE

Reference No.	Tissue	Potassium Content (mEq./kg.)	
		FFD Tissue*	Tissue Water
109	Skin (man, n=18)	58.5	23.0
67	Skin (man, n=2)	140.5	76.0
23	Tendon (dog, n=8)	41.1	20.5
102	Tendon (rat, n=20)	30.0	53.6
69	Cartilage (dog, n=13)	225 ± 3.3	77.3
67	Total skeleton (man, n=2)	52.2 (with marrow)	92.4
67	Tibia	24.3 (no marrow)	89.9
102	Bone cortex (rat, n=20)	20.0	111.0
66	Bone (man, n=37)	31.0	91.2

* FFD = fat-free dry weight of tissue.
† n = number of subjects

sium concentration of interstitial fluid and lymph, using the Gibbs-Donnan factor, 0.97, is 4.4 mEq. per L. Therefore, the total quantity of potassium in this phase, which averages 120 ml. per kg. of body weight, is 0.5 mEq. per kg. of body weight, or about 1 per cent of total body potassium in the healthy young adult.

Dense Connective Tissue, Cartilage and Bone Potassium. A comprehensive analysis of the potassium content of the extracellular aqueous phases of these tissues is not feasible in view of the small quantities involved; the maximum quantity of extracellular potassium in this phase is (4.4 × 45) or 0.2 mEq. per kg. of body weight. The reported data on the quantitations of potassium content of dense connective tissues and bone are listed in Table XVI. The total quantity of bone potassium averages 90 mEq. per kg. of tissue water or 4.1 mEq. per kg. of body weight or 7.6 per cent of total body potassium. This represents an unknown percentage of total exchangeable potassium, since exchangeability of bone potassium has not been evaluated. The extracellular fraction of bone potassium, exclusive of the free interstitial phase, may at most approach 0.2 mEq. per kg. of body weight, or 0.4 per cent of body potassium. It is probable that the bulk of the remaining potassium is adsorbed on the surface of bone crystals, while a small amount of bone potassium is intracellular.

Transcellular Fluid Potassium. Compared with sodium, there is somewhat less variation in potassium concentration of these fluids. (Table XII.) In those fluids in which it has been measured (urine and gastrointestinal fluid), radiopotassium seems to exchange completely with the transcellular potassium [*27,121,133*].

The intraluminal potassium of the gastrointestinal tract, as measured postmortem in man, ranges from 0.20 to 1.33 (mean = 0.44) mEq. per kg. of body weight [*27*]. The cerebrospinal fluid contains about 0.01 mEq. per kg. of body weight, while the other transcellular fluids contain even lesser quantities. The total transcellular potassium, therefore, is about 0.5 mEq. per kg. of body weight, or 1 per cent of total body potassium.

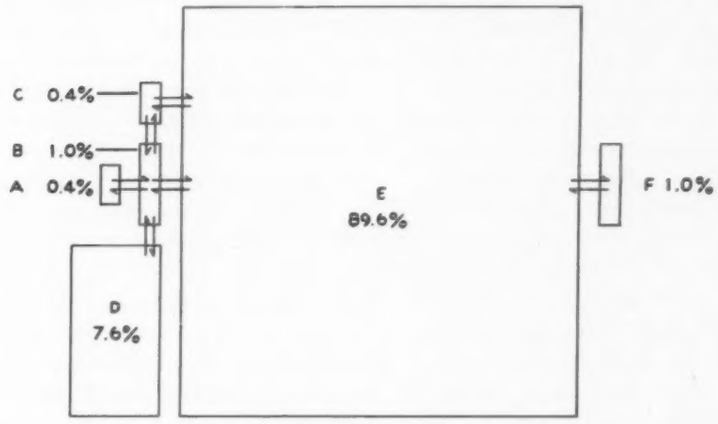
SUMMARY OF BODY POTASSIUM DISTRIBUTION

Table XVII and Figure 3 summarize the data on potassium distribution. The bulk of body potassium is intracellular, and in particular intramuscular. The calculated average intracellular potassium concentration is 48.3 mEq. per kg. of body weight, or 146 mEq. per L. of cell water (based on the estimate of 330 ml. of intracellular water per kg. of body weight). The latter figure is in close agreement with more direct calculations based on histochemical analyses [*134–136*]. (see Table XXI.) The organization, distribution and activity of intracellular potassium are currently a subject of active speculation and investigation. Considerable evidence has ac-

TABLE XVII
BODY POTASSIUM DISTRIBUTION IN AN "AVERAGE" NORMAL YOUNG ADULT MALE

	mEq./kg. of Body Weight	% of Total Exchangeable Potassium	% of Total Body Potassium
Plasma	0.2	0.4	0.4
Interstitial-lymph	0.5	1.0	1.0
Dense connective tissue and cartilage	0.2	0.4	0.4
Total bone	4.1	.....	7.6
Transcellular	0.5	1.0	1.0
Total extracellular	5.5	.....	10.4
Total body potassium*	53.8	110.0	100.0
Total intracellular	48.3	98.8	89.6

* Estimate is based on the assumption that the exchangeable potassium content of young males, 48.9 mEq./kg. of body weight (Table XV), is equal to 90 per cent of total body potassium.



A PLASMA POTASSIUM – 0.4% OF TOTAL BODY POTASSIUM
B INTERSTITIAL-LYMPH POTASSIUM – 1.0%
C DENSE CONNECTIVE TISSUE AND CARTILAGE POTASSIUM – 0.4%
D BONE POTASSIUM – 7.6%
E INTRACELLULAR POTASSIUM – 89.6%
F TRANSCELLULAR POTASSIUM – 1.0%

FIG. 3. Schematic diagram of body potassium distribution in a normal young adult man.

cumulated, demonstrating that intracellular potassium in various tissues exchanges at several different rates with outside media [*124,137,138*], implying that the status and activity of the potassium may vary depending on its location within the cell, the particular cell component with which it is associated, and the degree of binding to cell protein. In some tissues intracellular potassium concentration also varies somewhat from the mean, being lower in erythrocytes [*134*] and higher in brain [*117*]. The total extracellular potassium is about 5.5 mEq. per kg. of body weight, or 10.4 per cent of total body potassium; 75 per cent of this quantity resides in bone, leaving only 1.4 mEq. per kg. in the remaining extracellular fluids. Distortions of body potassium content and distribution with disease are frequent and vitally significant. There is no known naturally occurring condition associated with increased body potassium. Acute and chronic illness is almost invariably accompanied by losses of body potassium, which may reach 25 per cent of body content [*119*]. These losses are ordinarily not reflected by consistent changes in extracellular potassium concentration, unless losses have been acute or associated with changes in extracellular pH [*139*]. Hence, potassium losses are sustained primarily from the intracellular stores, and the body tends to maintain its extracellular potassium concentration preferentially. Isolated pH changes presumably invoke a change in distribution of potassium between intracellular and extracellular phases [*140*].

CHLORIDE CONTENT AND DISTRIBUTION

Since chloride is the primary anion of the plasma-interstitial fluids, there has been considerable interest in whether or not chloride is sufficiently restricted to these phases to be used as an index of extracellular fluid volume. Chloride has been shown by chemical analysis to be present in the intracellular water of erythrocytes, leukocytes, testis and gastric mucosa [*8,134,141*]. Mammalian skeletal muscle, on the other hand, appears to have little or no intracellular chloride, since the saccharide and chloride spaces approach unity if sufficient time is allowed for saccharide equilibration in muscle [*24*]. Inasmuch as muscle comprises about 40 per cent of body weight [*67*], the total intracellular chloride content should be small.

Total body chloride content has been estimated *in vivo* by the isotope dilution method, using either bromide[82], chloride[36] or chloride[38] as tracers, as well as stable bromide. Bromide was introduced as a tracer for chloride when it was found that its tissue distribution was substantially in proportion to tissue chloride content [*142,143*]. The exchangeable chloride content was estimated in dogs by stable bromide dilution and found to be 33.3 mEq. per kg. of body weight

[*144*], which agrees with the published figure of 33.6 mEq. per kg. of body weight obtained by chemical analysis of whole animals [*20*]. Where transport systems are involved, however, discrimination between bromide and chloride does occur. The bromide:chloride ratio of urine, brain and cerebrospinal fluid tends to be lower than the simultaneous bromide:chloride ratio of plasma [*145–147*] and somewhat higher in saliva and gastric juice [*147*] during the first twenty-four hours of equilibration. The intraluminal gastrointestinal fluids do, however, approach equilibrium of distribution after forty-eight hours [*28*], and the ratio of the simultaneous bromide^{82}:chloride^{38} volume of dilution is 1.03, with a range of 1.00 to 1.07 in man [*147*]. Therefore, bromide dilution provides reasonable estimates of *in vivo* exchangeable chloride content provided that sufficient time is allowed for equilibration.

The long half-life isotope chloride^{36} achieves a constant serum specific activity after forty-eight hours in normal man [*148*], presumably indicating equilibrium of distribution at this time. Studies on tissue:plasma specific activity ratios have not yet been carried out in man with this isotope, so that the exact relation between total exchangeable chloride estimated by this method and total body chloride is still unknown. The direct measurement of total body chloride in man gave figures of 34.2, 36.0 and 40.5 mEq. of chloride per kg. of body weight in three adult subjects [*67,84*]. The last figure may be abnormally high, since the chloride space in the skeletal muscle of this subject was 64 per cent of total skeletal water, a figure which is not approached in normal muscle.

TABLE XVIII
TOTAL EXCHANGEABLE CHLORIDE IN MAN

Reference No.	Method	Equilibration Time (hr.)	Age (yr.)	mEq./kg. of Body Weight
Males				
32, 127, 148, 149....	NaBr, Br^{82}	24	16–34 (n = 35)	31.0
32, 127, 145, 149....	NaBr, Br^{82}	5 and 24	35–50 (n = 24)	29.9
32, 127, 145.....	NaBr, Br^{82}	5 and 24	50+ (n = 11)	32.8
Females				
32, 127, 145, 148, 149	NaBr, Br^{82}	5 and 24	16–34 (n = 26)	28.0
127, 145.....	NaBr, Br^{82}	5 and 24	35–81 (n = 25)	27.8

The figures for total exchangeable chloride (obtained by bromide dilution) in man are listed in Table XVIII. Although no clear trend with age is discernible, the values are significantly higher in males than in females, approximately to the same extent as with total exchangeable sodium. (Table VIII.) In most series the individual values show a standard deviation of ± 3.5 mEq. per kg. of body weight, so that the values obtained by direct cadaver analysis fall within 2.5 standard deviations of the mean total exchangeable chloride for males of 31.5 mEq. per kg. of body weight. From the studies on long half-life chloride^{36} exchange, however, it appears probable that the twenty-four-hour exchangeable chloride underestimates total body chloride by about 5 per cent and that the best estimate for average total body chloride in normal adult males is 33.0 mEq. per kg. of body weight.

The partition of body chloride among plasma, interstitial-lymph, dense connective tissue, cartilage and bone, transcellular fluid and intracellular fluid reveals that while the intracellular chloride pool is small, there are sizable quantities of chloride outside the plasma-interstitial fluid-lymph phases.

Plasma Chloride. The plasma chloride concentration tends to vary slightly with age and sex; the values are 104.9 ± 4.7 mEq. per L. in infants, 103.3 ± 3.0 in children, 100.2 ± 2.4 in adult males and 102.3 ± 2.9 in adult females [*104*]. The mean total plasma chloride content, therefore, is 4.5 and 4.4 mEq. per kg. of body weight in young adult males and females, respectively. As with sodium and potassium, the range of total plasma chloride in normal subjects is very wide. It may be as little as 200 mEq. in a female or as much as 450 mEq. in a male.

Compared with sodium, plasma chloride represents a larger fraction of the total body content, averaging 14.5 per cent of total exchangeable chloride or 13.6 per cent of the estimated total body chloride content in normal adult males. Total plasma chloride content may change under pathophysiological circumstances, independent of changes in plasma volume, since hyperchloremia may appear in some varieties of metabolic acidosis, and hypochloremia often is present in patients with either respiratory acido-

sis or metabolic alkalosis. Total plasma chloride content, of course, will vary *pari passu* with alterations in plasma volume.

Interstitial-Lymph Fluid Chloride. The distribution of chloride between plasma and ultrafiltrates of plasma accords with the Gibbs-Donnan principle both *in vivo* and *in vitro* [*10*]. The concentration ratio of transudate chloride: plasma chloride for transudates containing less than 1 per cent protein in man is 1.03, and for transudates containing more than 1 per cent protein is 1.01. Table IX summarizes the data on plasma chloride and the partition of chloride between plasma, interstitial fluid and lymph. The average normal interstitial-lymph chloride concentration is 103 ± 2.5 mEq. per L., and the mean chloride content of this phase in adult males is 12.3 mEq. per kg. of body weight; this represents 39.7 per cent of total exchangeable chloride, or 37.3 per cent of total body chloride. The combined plasma-interstitial-lymph chloride amounts to approximately 50 per cent of total body chloride. This estimate is lower than the figures derived from simultaneous sodium bromide and sucrose dilution studies in which the chloride content of the saccharide volume of dilution averaged 70 per cent of exchangeable chloride [*32*]. It is highly probably that the chloride of the interstitial-lymph phase is freely mobile, since it has been shown that viviperfusion with chloride-free Ringer's solution produces proportional reductions in tissue chloride content except in brain, spleen and gastric mucosa [*150*].

Dense Connective Tissue, Cartilage and Bone Chloride. It has been demonstrated that dense connective tissues such as tendon have less water and more chloride than other soft tissues [*68,70*]. The concentration ratio of tendon chloride: serum chloride has been reported as 1.14 and 1.08 in rabbits and dogs respectively. Similarly, the calculated concentration of chloride in the connective tissue water of human skin is 129.4 ± 7.5 mEq. per L., which is distinctly higher than the chloride concentration in an ultrafiltrate of plasma [*109*]. The presence of chloride outside the free interstitial fluid of these tissues is also suggested by the fact that there is a disproportionate retention of chloride in skin when the plasma chloride is markedly reduced [*150,151*]. These data suggest that chloride may be bound to the extracellular proteins of connective tissue, since chloride binding by albumin has been demonstrated [*152*]. This may result from either acid binding by protein, complex binding, or electrostatic binding as a "gegen" ion to bound cations [*153*].

Table XIX lists the chloride content and concentrations in dense connective tissues, cartilage and bone. The total quantity in these tissues is approximately (129 × 40) or 5.2 and (70 × 5) or 0.4 mEq. per kg. of body weight in tendon and cartilage, respectively. This quantity, 5.6 mEq. per kg. of body weight, constitutes 17.8 per cent of average exchangeable chloride in the adult male, or 17.0 per cent of total body chloride.

Bone chloride is apparently extracellular, and chloride concentration in bone water is in accord with the relative acellularity of this tissue. The total skeletal chloride measured in two cadavers was 6.5 and 4.4 mEq. per kg. of body weight [*67*]. From the data based on sampling of bone aliquots and presented in Tables XIX and XX, the calculated bone chloride content is 4.3 mEq. per kg. of body weight, which is in reasonable agreement with the total skeletal analysis. A figure of 5.0 mEq. of bone chloride per kg. of body weight approximates all the available data, and this quantity is 15.9 per cent of exchangeable chloride, or 15.2 per cent of total body chloride.

Transcellular Fluid Chloride. The chloride concentration of the transcellular fluids is quite variable. In many instances the concentrations vary with changes in rates of secretion or with other physiological parameters [*112,115,154*]. Table XII lists characteristic chloride concentra-

TABLE XIX

CHLORIDE CONTENT OF DENSE CONNECTIVE TISSUE, CARTILAGE AND BONE

Reference No.	Tissue	mEq./kg. of FFD Weight*	mEq./L. of Tissue Water	mEq./kg. of Wet Weight Tissue
109	Skin—connective tissue phase (man, n = 14)†	63.7 ± 6.6	129.4 ± 7.5	42.7 ± 5.7
23	Tendon (dog, n = 8)	257.9	128.8	85.9
70	Tendon (rabbit, n = 14)	195.5	121.0 ± 10.9	74.7
69	Cartilage (puppy, n = 13)	220.8	71.6	54.1 ± 1.8
68	Cartilage‡ (man, n = 7)	161.7	65.5	46.5 ± 4.5
67	Total skeleton (man, n = 2)	46.7	119.3	33.5
21, 66, 68	Bone (man, n = 58)	36.0	100.1	24.1

* Fat-free dry weight of tissue.
† n = number of subjects.
‡ Tissue samples taken postmortem without marrow.

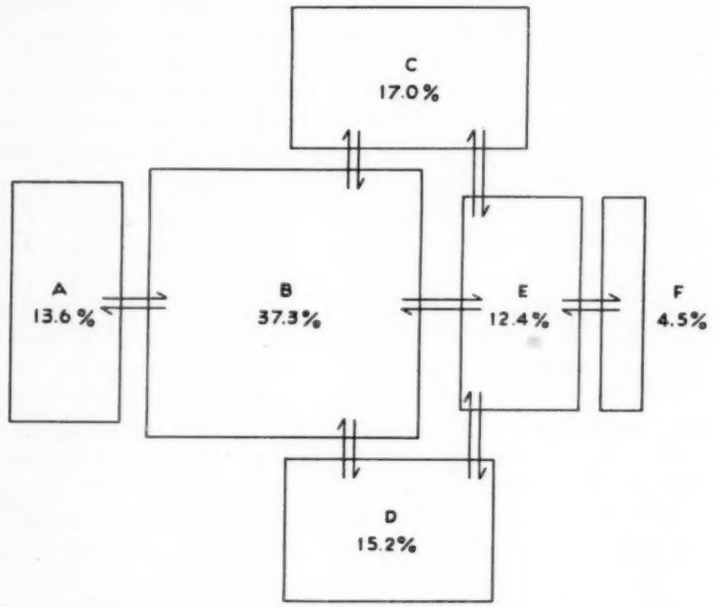


FIG. 4. Schematic diagram of body chloride distribution in a normal young adult man.

tions for some of the transcellular fluids in man. The largest component, intraluminal gastrointestinal chloride, has been measured directly in man at postmortem examination [*28*]. These estimates indicate a mean of 0.6 mEq. of chloride per kg. of body weight, with a range of 0.3 to 1.1 mEq. per kg. The wide range of values reflects the dependence of this quantity on the variable physiological processes of absorption and secretion, bearing in mind the limitations of data collected postmortem. Species differences are quite marked; in the fasting rabbit, for example, the intraluminal chloride averages 5.8 mEq. per kg. of body weight [*28*]. The average total chloride in cerebrospinal fluid and bile calculated from Tables V and XII is 0.4 and 0.2 mEq. per kg., respectively.

TABLE XX
DISTRIBUTION OF BODY CHLORIDE IN ADULT MAN

	mEq./kg. of Body Weight	% of Total Exchangeable Chloride	% of Total Body Chloride
Plasma	4.5	14.5	13.6
Interstitial-lymph	12.3	39.7	37.3
Dense connective tissue and cartilage	5.6	17.8	17.0
Bone	5.0	15.9	15.2
Transcellular	1.5	4.8	4.5
Total extracellular	28.9	92.7	87.6
Total bdoy chloride	33.0	104.8	100.0
Total intracellular	4.1	13.0	12.4

TABLE XXI
HISTOCHEMICAL ESTIMATIONS OF INTRACELLULAR ELECTROLYTE CONCENTRATIONS

Reference No.	Source	Sodium	Potassium	Chloride
		mEq./L. of Cell Water	mEq./L. of Cell Water	mEq./L. of Cell Water
134	Erythrocyte (man)	22.2 ± 2.0	138.0 ± 4.5	77.8 ± 4.6
135	Skeletal muscle (man)	26.1 ± 12.6	150.0 ± 11.0	.....
136	Skeletal muscle (man)	.....	153.0	.....
156	Skeletal muscle (man)	8.0	156.7	.....
155	Cardiac muscle (cat)	5.0	151.0	.....
117	Brain (dog)	15.0	205.0	.....
116	Liver (dog)	3.0	161.0	.....

Based on the estimated volume of the remainder of the transcellular fluids and their characteristic chloride concentrations, and the values calculated for gut, cerebrospinal fluid and bile chloride, total transcellular fluid chloride is approximately 1.5 mEq. per kg. of body weight. This represents 4.8 and 4.5 per cent of exchangeable chloride and total body chloride, respectively. In pathological states the translocation of fluid and electrolyte into the gut may double or even triple this quantity [*113*].

SUMMARY OF BODY CHLORIDE DISTRIBUTION

Table xx and Figure 4 summarize the distribution of chloride among the body fluids. The calculated average intracellular chloride is 4.1 mEq. per kg. of body weight, or 12.3 mEq. per L. of cell water, which agrees well with the small amounts estimated histochemically [*5,8,24*]. The chloride content of erythrocytes, leukocytes and the tissues which elaborate external secretions, such as the salivary glands, gastrointestinal mucosa and testes, presumably accounts for the quantity of intracellular chloride derived in Table xx. In the resting salivary gland, for example, the average composition is 85 mEq. of potassium, 35 mEq. of sodium, and 54 mEq. of chloride per kg. of wet weight [*10*]. The ratio of chloride:sodium in gastric mucosa has been reported as 2:1 [*8*]. These data presumably indicate a significant fraction of intracellular chloride in these tissues. Other secretory tissues, such as the pancreas, sweat glands and mucous glands of the respiratory tract, probably contain similar quantities of intracellular chloride. In general, changes in body chloride content are effected by the same factors and in the same direction as sodium, while the distribution may be significantly altered by changes in extracellular pH.

COMMENTS

Table xxi lists some representative histochemical estimates of intracellular electrolyte concentrations of various tissues, corrected for fat, blood and chloride content, except for erythrocytes, which were directly analyzed. When intracellular sodium and potassium content are compared with the indirect estimates derived in Tables xiii and xvii, there is good agreement between the figures. It is believed that our indirect methods of analyzing and describing the content and distribution of water and electrolytes in the body lead to accurate estimations, based on data which have been integrated from a variety of sources and technics, and provides reasonable correlations of histochemical and isotope dilution data. The resultant depiction of the anatomy of body water and electrolytes represents a revision of some older concepts. The evolution of newer and more accurate technics will undoubtedly lead to further refinement, definition and extension of these concepts.

REFERENCES

1. Moore, F. D. Determination of total body water and solids with isotopes. *Science*, 104: 157, 1946.
2. Edelman, I. S., Olney, J. M., James, A. H., Brooks, L. and Moore, F. D. Body composition: studies in the human being by the dilution principle. *Science*, 115: 447, 1952.
3. Gamble, J. L. Companionship of water and electrolytes in the organization of body fluids. Lane Medical Lectures. Stanford, 1951. Stanford University Press.
4. Gersh, I. Improved histochemical methods for chloride, phosphate, carbonate and potassium applied to skeletal muscle. *Anat. Rec.*, 70: 311, 1938.
5. Hastings, A. B. The electrolytes of tissues and body fluids. *Harvey Lect.*, p. 91, 1940–1941.
6. Fenn, W. O. Electrolytes in muscle. *Physiol. Rev.*, 16: 450, 1936.
7. Peters, J. P. Transfers of water and solutes in the body. *Harvey Lect.*, p. 112, 1937–1938.
8. Manery, J. F. and Hastings, A. B. The distribution of electrolytes in mammalian tissues. *J. Biol. Chem.*, 127: 657, 1939.
9. Pappenheimer, J. R., Renkin, E. M. and Borrero, L. M. Filtration, diffusion and molecular sieving through peripheral capillary membranes. *Am. J. Physiol.*, 167: 13, 1951.
10. Manery, J. F. Water and electrolyte metabolism. *Physiol. Rev.*, 34: 334, 1954.
11. Overman, R. R. Sodium, potassium and chloride alterations in disease. *Physiol. Rev.*, 31: 285, 1951.
12. Winkler, A. W., Elkinton, J. R. and Eisenman, A. Comparison of sulfocyanate with radioactive chloride and sodium in the measurement of extracellular fluid. *Am. J. Physiol.*, 139: 239, 1943.
13. Brodie, B. B., Brand, E. and Leshin, S. The use of bromide as a measure of extracellular fluid. *J. Biol. Chem.*, 130: 555, 1939.
14. Lavietes, P. H., Bourdillon, J. and Klinghoffer, K. A. The volume of the extracellular fluids of the body. *J. Clin. Invest.*, 15: 261, 1936.
15. Gilman, A., Philips, F. S. and Koelle, E. S. Renal clearance of thiosulfate with observations on its volume distribution. *Am. J. Physiol.*, 146: 348, 1946.
16. Bourdillon, J. and Lavietes, P. H. Observations on the fate of sodium sulfate injected intravenously in man. *J. Clin. Invest.*, 15: 301, 1936.
17. Calcagno, P. L., Husson, G. S. and Rubin, M. I. Measurement of "extracellular fluid space" in infants by equilibration technic using inulin and

sodium ferrocyanide. *Proc. Soc. Exper. Biol. & Med.*, 77: 309, 1951.

18. Newman, E. V., Bordley, J. and Winternitz, J. The interrelationships of glomerular filtration rate (mannitol clearance), extracellular fluid volume, surface area of the body and plasma concentration of mannitol. *Bull. Johns Hopkins Hosp.*, 75: 253, 1944.
19. Kruhøffer, P. Inulin as an indicator for the extracellular space. *Acta physiol. Scandinav.*, 11: 16, 1946.
20. Harrison, H. E., Darrow, D. C. and Yannet, H. The total electrolyte content of animals and its probable relation to the distribution of body water. *J. Biol. Chem.*, 113: 515, 1936.
21. Edelman, I. S., James, A. H., Baden, H. and Moore, F. D. Electrolyte composition of bone and the penetration of radiosodium and deuterium oxide into dog and human bone. *J. Clin. Invest.*, 33: 122, 1954.
22. Bergstrom, W. H. and Wallace, W. M. Bone as a sodium and potassium reservoir. *J. Clin. Invest.*, 33: 867, 1954.
23. Nichols, G., Jr., Nichols, N., Weil, W. B. and Wallace, W. M. The direct measurement of the extracellular phase of tissues. *J. Clin. Invest.*, 32: 1299, 1953.
24. Cotlove, E. Mechanism and extent of distribution of inulin and sucrose in chloride space of tissues. *Am. J. Physiol.*, 176: 396, 1954.
25. Cizek, L. J. Total water content of laboratory animals with special reference to volume of fluid within the lumen of the gastrointestinal tract. *Am. J. Physiol.*, 179: 104, 1954.
26. Edelman, I. S. and Sweet, N. J. Gastrointestinal water and electrolytes. I. The equilibration of radiosodium in gastrointestinal contents and the proportion of exchangeable sodium (Na_e) in the gastrointestinal tract. *J. Clin. Invest.*, 35: 502, 1956.
27. Nadell, J., Sweet, N. J. and Edelman, I. S. Gastrointestinal water and electrolytes. II. The equilibration of radiopotassium in gastrointestinal contents and the proportion of exchangeable potassium (K_e) in the gastrointestinal tract. *J. Clin. Invest.*, 35: 512, 1956.
28. Sweet, N. J., Nadell, J. and Edelman, I. S. Gastrointestinal water and electrolytes. III. The equilibration of radiobromide in gastrointestinal contents and the proportion of exchangeable chloride (Cl_e) in the gastrointestinal tract. *J. Clin. Invest.*, 36: 279, 1957.
29. Gotch, F., Nadell, J. and Edelman, I. S. Gastrointestinal water and electrolytes. IV. The equilibration of deuterium oxide (D_2O) in gastrointestinal contents and the proportion of total body water (T.B.W.) in the gastrointestinal tract. *J. Clin. Invest.*, 36: 289, 1957.
30. Levitt, M. F. and Gaudino, M. Use of radioactive isotopes to measure intracellular cation concentrations in the normal dog. *Am. J. Physiol.*, 159: 67, 1949.
31. Deane, N. and Smith, H. W. The distribution of sodium and potassium in man. *J. Clin. Invest.*, 31: 197, 1952.
32. Deane, N., Ziff, M. and Smith, H. W. The distribution of total body chloride in man. *J. Clin. Invest.*, 31: 200, 1952.
33. Cardozo, R. H. and Edelman, I. S. The volume of distribution of thiosulfate as a measure of extracellular fluid space. *J. Clin. Invest.*, 31: 280, 1952.
34. Bischoff, E. Einige Gewichts und Trocken-Bestimmungen der Organe des menschlichen Körpers. *Ztschr. f. rat. Med.*, 20: 75, 1863.
35. Volkman, A. M. Handbuch der Physiologie. Quoted in Voit, vol. 6, p. 345. Leipzig, 1881.
36. Camerer, W., Söldner and Herzog. Die chemische Zusammensetzung des Neugeborenen. *Ztschr. f. Biol.*, 43: 1, 1902.
37. Schloerb, P. R., Friis-Hansen, B. J., Edelman, I. S., Sheldon, D. B. and Moore, F. D. The measurement of total body water in the human subject by deuterium oxide dilution. *J. Clin. Invest.*, 29: 1296, 1950.
38. Edelman, I. S. Exchange of water between blood and tissues. Characteristics of deuterium oxide equilibration in body water. *Am. J. Physiol.*, 171: 279, 1952.
39. Pace, N., Kline, L., Schachman, H. K. and Harfenist, M. Studies on body composition. IV. Use of radioactive hydrogen for measurement in vivo of total body water. *J. Biol. Chem.*, 168: 459, 1947.
40. Brodie, B. B. Methods in Medical Research, vol. 4, p. 31. New York, 1951. Academic Press.
41. Osserman, E. F., Pitts, G. C., Welham, W. C. and Behnke, A. R. In vivo measurement of body fat and body water in a group of normal men. *J. Appl. Physiol.*, 2: 633, 1950.
42. Keys, A. and Brożek, J. Body fat in adult man. *Physiol. Rev.*, 33: 245, 1953.
43. Prentice, T. C., Siri, W., Berlin, N. I., Hyde, G. M., Parsons, R. J., Joiner, E. E. and Lawrence, J. H. Studies of total body water with tritium. *J. Clin. Invest.*, 31: 412, 1952.
44. Soberman, R. J., Brodie, B. B., Levy, B. B., Axelrod, J., Hollander, V. and Steele, J. M. The use of antipyrine in the measurement of total body water in man. *J. Biol. Chem.*, 179: 31, 1949.
45. Friis-Hansen, B. J., Holiday, M., Stapleton, T. and Wallace, W. M. Total body water in children. *Pediatrics*, 7: 321, 1951.
46. Messinger, W. J. and Steele, J. M. Relationship of body specific gravity to body fat and water content. *Proc. Soc. Exper. Biol. & Med.*, 70: 316, 1949.
47. Leibman, J., Gotch, F. A. and Edelman, I. S. Unpublished observations.
48. Edelman, I. S., Haley, H. B., Schloerb, P. R., Sheldon, D. B., Friis-Hansen, B. J., Stoll, G. and Moore, F. D. Further observations on total body water. I. Normal values throughout the life span. *Surg., Gynec. & Obst.*, 95: 1, 1952.
49. Friis-Hansen, B. Changes in body water compartments during growth. *Acta paediat.*, (supp. 110) 46: 1–68, 1957.
50. Steele, J. M., Berger, E. Y., Dunning, M. F. and Brodie, B. B. Total body water in man. *Am. J. Physiol.*, 162: 313, 1950.
51. Wallace, W. M. Some aspects of the chemical composition, physiology and pathology of intracellular fluid. *Pediatrics*, 9: 141, 1952.

52. Gregersen, M. I. Blood volume. *Ann. Rev. Physiol.*, 13: 397, 1951.
53. Sjöstrand, T. Volume and distribution of blood and their significance in regulating the circulation. *Physiol. Rev.*, 33: 202, 1953.
54. Brown, E., Hopper, J., Jr. and Wennesland, R. Blood volume and its regulation. *Ann. Rev. Physiol.*, 19: 231, 1957.
55. Berson, S. A. and Yalow, R. S. The use of K^{42} or P^{32} labeled erythrocytes and I^{131} tagged human serum albumin in simultaneous blood volume determinations. *J. Clin. Invest.*, 31: 572, 1952.
56. Chaplin, H., Jr., Mollison, P. L. and Vetter, H. The body/venous hematocrit ratio: its constancy over a wide hematocrit range. *J. Clin. Invest.*, 32: 1309, 1953.
57. Berson, S. A. Blood volume in health and disease. *Bull. New York Acad. Med.*, 30: 750, 1954.
58. Reeve, E. B. Methods of estimating plasma and total red cell volume. *Nutrition Abstr. & Rev.*, 17: 811, 1948.
59. von Porat, B. Blood volume determinations with Evans blue dye method. *Acta med. Scandinav.*, (supp. 256) 140: 1–108, 1951.
60. Allen, T. H., Peng, M. T., Chen, F. P., Huang, T. F., Chang, C. and Fang, H. S. Prediction of blood volume and adiposity in man from body weight and cube of height. *Metabolism*, 5: 328, 1956.
61. Gibson, J. G., II and Evans, W. A., Jr. Clinical studies of the blood volume; the relation of plasma and total blood volume to venous pressure, blood velocity rate, physical measurements, age and sex in ninety normal humans. *J. Clin. Invest.*, 16: 317, 1937.
62. Pappenheimer, J. R. Passage of molecules through capillary walls. *Physiol. Rev.*, 33: 387, 1953.
63. Schwartz, I. L., Breed, E. S. and Maxwell, M. H. Comparison of the volume of distribution, renal and extrarenal clearances of inulin and mannitol in man. *J. Clin. Invest.*, 29: 517, 1950.
64. Deane, N. Intracellular water in man. *J. Clin. Invest.*, 30: 1469, 1951.
65. Neuman, W. F. and Neuman, M. W. The nature of the mineral phase of bone. *Chem. Rev.*, 53: 1, 1953.
66. Agna, J. W., Knowles, H. C., Jr. and Alverson, G. The mineral content of normal human bone. *J. Clin. Invest.*, 37: 1357, 1958.
67. Forbes, G. B. and Lewis, A. M. Total sodium, potassium and chloride in adult man. *J. Clin. Invest.*, 35: 596, 1956.
68. Close, H. G. Chloride and water in the constitution of tissues. *Biochem. J.*, 27: 967, 1933.
69. Eichelberger, L., Brower, T. D. and Roma, M. Histochemical characterization of inorganic constituents, connective tissue and the chondroitin sulfate of extracellular and intracellular compartments of hyaline cartilage. *Am. J. Physiol.*, 166: 328, 1951.
70. Manery, J. F., Danielson, I. S. and Hastings, A. B. Connective tissue electrolytes. *J. Biol. Chem.*, 124: 359, 1938.
71. Brown, H. The mineral content of human skin. *J. Biol. Chem.*, 75: 789, 1927.
72. Lightfoot, L. H. and Coolidge, T. B. The distribution of collagen in the guinea pig. *J. Biol. Chem.*, 176: 477, 1948.
73. Neuman, W. F. and Neuman, M. W. Emerging concepts of the structure and metabolic functions of bone. *Am. J. Med.*, 22: 123, 1957.
74. Kleeman, C. R., Epstein, F. H., Rubini, M. E. and Lamdin, E. Initial distribution and fate of ferrocyanide in dogs. *Am. J. Physiol.*, 182: 548, 1955.
75. Crandall, L. A. and Anderson, M. X. Estimation of the state of hydration of the body by the amount of water available for the solution of sodium thiocyanate. *Am. J. Digest. Dis.*, 1: 126, 1934.
76. Gregersen, M. I. and Wright, L. The effect of intravenous injection of sucrose and glucose upon the reducing power of cerebrospinal fluid, before and after hydrolysis. *Am. J. Physiol.*, 112: 97, 1935.
77. Mokotoff, R., Ross, G. and Leiter, L. The electrolyte content of skeletal muscle in congestive heart failure; a comparison of results with inulin and chloride as reference standards for extracellular water. *J. Clin. Invest.*, 31: 291, 1952.
78. Lups, S. and Haan, A. M. F. H. The Cerebrospinal Fluid. Amsterdam, 1954. Elsevier Press.
79. Miller, H. and Wilson, G. M. The measurement of exchangeable sodium in man using the isotope Na^{24}. *Clin. Sc.*, 12: 97, 1953.
80. Forbes, G. B. and Perley, A. Estimation of total body sodium by isotopic dilution. I. Studies on young adults. *J. Clin. Invest.*, 30: 558, 1951.
81. Edelman, I. S., James, A. H., Brooks, L. and Moore, F. D. Body sodium and potassium. IV. The normal exchangeable sodium, its measurement and magnitude. *Metabolism*, 3: 530, 1954.
82. O'Meara, M. P., Birkenfeld, L. W., Gotch, F. A. and Edelman, I. S. The equilibration of radiosodium (Na^{24}), radiopotassium (K^{42}) and deuterium oxide (D_2O) in hydropic human subjects. *J. Clin. Invest.*, 36: 784, 1957.
83. Miller, H., Munro, D. S., Renschler, H. E. and Wilson, G. M. Observations on the measurement and distribution of exchangeable sodium in man. In: Proceedings of the Second Radioisotope Conference, p. 138. Oxford, 1954. Butterworth Scientific Publications.
84. Shohl, A. T. Mineral Metabolism. New York, 1939. Reinhold Publishing Corp.
85. Widdowson, E. M., McCance, R. A. and Spray, C. M. The chemical composition of the human body. *Clin. Sc.*, 10: 113, 1951.
86. McLean, F. C. and Urist, M. R. Bone. An Introduction to the Physiology of Skeletal Tissue. Chicago, 1955. University of Chicago Press.
87. Davies, R. E., Kornberg, H. L. and Wilson, G. M. Non-exchangeable sodium in the body. *Biochim. et biophys. acta*, 9: 703, 1952.
88. Christian, J. R., Talso, P. J., Karezeris, M. P., Spafford, N. R., Jackson, H. and Larsen, M. Total body water and exchangeable sodium in normal full term newborn infants. *J. Dis. Child.*, 92: 325, 1956.
89. Ikkos, D., Luft, R. and Sjögren, B. The distribution of fluid and sodium in healthy adults. *Metabolism*, 3: 400, 1954.
90. Warner, G. F., Dobson, E. L., Rodgers, C. E.,

JOHNSTON, M. E. and PACE, N. The measurement of total "sodium space" and total body sodium in normal individuals and in patients with cardiac edema. *Circulation*, 5: 915, 1952.

91. TALSO, P. J., SPAFFORD, N., FERENZI, G. and JACKSON, H. O. Paradoxical hyponatremia associated with congestive heart failure and with cirrhosis of the liver. *Metabolism*, 5: 58, 1956.
92. DE GRAEFF, J. Inulin space and total exchangeable sodium in patients with essential hypertension. *Acta med. Scandinav.*, 156: 337, 1957.
93. ROSS, E. J. Total exchangeable sodium in hypertensive patients. *Clin. Sc.*, 15: 81, 1956.
94. ROBINSON, C. V., ARONS, W. L. and SOLOMON, A. K. An improved method for simultaneous determination of exchangeable body sodium and potassium. *J. Clin. Invest.*, 34: 134, 1955.
95. ARONS, W. L., VANDERLINDE, R. J. and SOLOMON, A. K. II. The simultaneous measurement of exchangeable body sodium and potassium utilizing ion exchange chromatography. *J. Clin. Invest.*, 33: 1001, 1954.
96. GILDER, H., REDO, S. F., BARR, D. and CHILD, C. G., III. Water distribution in normal subjects and in patients with Laennec's cirrhosis. *J. Clin. Invest.*, 33: 555, 1954.
97. WARNER, G. F. Personal communication.
98. ARONS, W. L., NUSIMOVICH, B., VANDERLINDE, R. J. and THORN, G. W. Effect of exogenous adrenocortical hormones and states of adrenal dysfunction on body sodium and potassium composition. *J. Clin. Endocrinol.*, 18: 611, 1958.
99. SPECTOR, W. S. Handbook of Biological Data, p. 52. Philadelphia, 1956. W. B. Saunders Co.
100. ELKINTON, J. R. and DANOWSKI, T. S. The Body Fluids. Basic Physiology and Practical Therapeutics. Baltimore, 1955. Williams & Wilkins Co.
101. BERGSTROM, W. H. The participation of bone in total bone sodium metabolism in the rat. *J. Clin. Invest.*, 34: 997, 1955.
102. LEVITT, M. F., TURNER, L. B., SWEET, A. Y. and PANDIRI, D. The response of bone, connective tissue and muscle to acute acidosis. *J. Clin. Invest.*, 35: 98, 1956.
103. NICHOLS, G., JR. and NICHOLS, N. Changes in tissue composition during acute sodium depletion. *Am. J. Physiol.*, 186: 383, 1956.
104. BAUER, G. C. H. Metabolism of bone sodium in rats investigated with Na^{22}. *Acta physiol. Scandinav.*, 31: 334, 1954.
105. TARAIL, R., HACKER, E. S. and TAYMOR, R. The ultrafiltrability of potassium and sodium in human serum. *J. Clin. Invest.*, 31: 23, 1952.
106. BIERMAN, H. R., BYRON, R. L., JR., KELLY, K. H., GILFILLAN, R. S., WHITE, L. P., FREEMAN, N. E. and PETRAKIS, N. L. The characteristics of thoracic duct lymph in man. *J. Clin. Invest.*, 32: 637, 1953.
107. YOFFEY, J. M. and COURTICE, F. C. Lymphatics, Lymph and Lymphoid Tissue, p. 243. London, 1956. E. Arnold, Ltd.
108. DAVIES, R. E., KORNBERG, H. L. and WILSON, G. M. The determination of sodium in bone. *Biochem. J.*, 52: 15, 1952.
109. EISELE, C. W. and EICHELBERGER, L. Water, electrolyte and nitrogen content of human skin. *Proc. Soc. Exper. Biol. & Med.*, 58: 97, 1945.
110. MONTGOMERY, M. L., SHELINE, G. E. and CHAIKOFF, I. L. Elimination of sodium in pancreatic juice as measured by radioactive sodium. *Am. J. Physiol.*, 131: 578, 1941.
111. SELVERSTONE, B. Studies of the formation and absorption of the cerebrospinal fluid using radioactive isotopes. In: The Cerebrospinal Fluid, p. 147. Edited by Wolstenholme, G. E. W. and O'Connor, C. M. London, 1958. J. & A. Churchill, Ltd.
112. WHITE, A. G., GORDON, H. and LEITER, L. Studies in edema. II. The effect of congestive heart failure on saliva electrolyte concentrations. *J. Clin. Invest.*, 29: 1445, 1950.
113. LOCKWOOD, J. S. and RANDALL, H. T. The place of electrolyte studies in surgical patients. *Bull. New York Acad. Med.*, 25: 228, 1949.
114. KINSEY, E. V. The chemical composition and the osmotic pressure of the aqueous humor and plasma of the rabbit. *J. Gen. Physiol.*, 34: 389, 1951.
115. ROBINSON, S. and ROBINSON, A. H. Chemical composition of sweat. *Physiol. Rev.*, 34: 202, 1954.
116. EICHELBERGER, L. and MCLEAN, F. C. The distribution of calcium and magnesium between the cells and the extracellular fluids of skeletal muscle and liver in dogs. *J. Biol. Chem.*, 142: 467, 1942.
117. EICHELBERGER, L. and RICHTER, R. B. Water, nitrogen and electrolyte concentration in brain. *J. Biol. Chem.*, 154: 21, 1944.
118. SOLOMON, A. K. Permeability of the human erythrocyte to sodium and potassium. *J. Gen. Physiol.*, 36: 57, 1952.
119. BIRKENFELD, L. W., LEIBMAN, J., O'MEARA, M. P. and EDELMAN, I. S. Total exchangeable sodium, total exchangeable potassium and total body water in edematous patients with cirrhosis of the liver and congestive heart failure. *J. Clin. Invest.*, 37: 687, 1958.
120. LIPSETT, M. B. and PEARSON, O. H. Sodium depletion in adrenalectomized humans. *J. Clin. Invest.*, 37: 1394, 1958.
121. CORSA, L., OLNEY, J. M., STEENBURG, R. W., BALL, M. R. and MOORE, F. D. The measurement of exchangeable potassium in man by isotope dilution. *J. Clin. Invest.*, 29: 1280, 1950.
122. RUNDO, J. and SAGILD, U. Total and "exchangeable" potassium in humans. *Nature, London*, 175: 774, 1955.
123. FENN, W. O., NOONAN, T. R., MULLINS, L. J. and HAEGE, L. F. The exchange of radioactive potassium with body potassium. *Am. J. Physiol.*, 135: 149, 1941.
124. WILDE, W. S., GINSBERG, S. and WALKER, W. G. The distribution kinetics of intravenous potassium. *Journal-Lancet*, 73: 168, 1953.
125. CORSA, L., JR., GRIBETZ, D., COOK, C. and TALBOT, N. Total body exchangeable water, sodium and potassium in "hospital normal" infants and children. *Pediatrics*, 17: 184, 1956.
126. SAGILD, U. Total exchangeable potassium in normal subjects with special reference to changes

with age. *Scandinav. J. Clin. & Lab. Invest.*, 8: 44, 1956.

127. Muldowney, F. P., Crooks, J. and Bluhm, M. M. The relationship of total exchangeable potassium and chloride to lean body mass, red cell mass and creatinine excretion in man. *J. Clin. Invest.*, 36: 1375, 1957.
128. Woodward, K. T., Trujillo, T. T., Schuch, R. L. and Anderson, E. C. Correlation of total body potassium with body water. *Nature, London*, 178: 97, 1956.
129. Ljunggren, H., Ikkos, D. and Luft, R. Studies on body composition. I. Body fluid compartments and exchangeable potassium in normal males and females. *Acta endocrinol.*, 25: 187, 1957.
130. Ikkos, D., Ljunggren, H., Luft, R. and Sjögren, B. Content and distribution of potassium and chloride in adults. *Metabolism*, 4: 231, 1955.
131. Aikawa, J. K., Harrell, G. T. and Eisenberg, B. The exchangeable potassium content of normal women. *J. Clin. Invest.*, 31: 367, 1952.
132. Folk, B. P., Zierler, K. C. and Lilienthal, J. L., Jr. Distribution of potassium and sodium between serum and certain extracellular fluids in man. *Am. J. Physiol.*, 153: 381, 1948.
133. Eisenman, A. J., Smith, P. K., Winkler, A. W. and Elkinton, J. R. Transfer of ions across stomach wall studied by means of radioactive isotopes. *J. Biol. Chem.*, 140: 35, 1941.
134. Keitel, H. G., Berman, H., Jones, H. and MacLachlan, E. Chemical composition of normal human red blood cells, including variability among centrifuged cells. *Blood*, 10: 370, 1955.
135. Barnes, B. A., Gordon, E. B. and Cope, O. Skeletal muscle analyses in health and in certain metabolic disorders. I. The method of analysis and the values in normal muscle. *J. Clin. Invest.*, 36: 1239, 1957.
136. Talso, P. J., Spafford, N. and Blaw, M. Metabolism of water and electrolytes in congestive heart failure. I. Electrolyte and water content of normal human skeletal muscle. *J. Lab. & Clin. Med.*, 41: 281, 1953.
137. Bozler, E., Calvin, M. E. and Watson, D. W. Exchange of electrolytes in smooth muscle. *Am. J. Physiol.*, 195: 38, 1958.
138. Harris, E. J. Transport and Accumulation in Biological Systems, p. 172. London, 1956. Butterworth Scientific Publications.
139. Moore, F. D., Boling, E. A., Ditmore, H. B., Siculer, A., Teterick, J. E., Ellison, A. E., Hoye, S. J. and Ball, M. R. Body sodium and potassium. V. The relationship of alkalosis, potassium deficiency, and surgical stress to acute hypokalemia in man. *Metabolism*, 4: 379, 1955.
140. Burnell, J. M., Villamil, M. F., Uyeno, B. T. and Scribner, B. H. The effect in humans of extracellular pH change on the relationship between serum potassium concentration and intracellular potassium. *J. Clin. Invest.*, 35: 935, 1956.
141. Wilson, D. L. and Manery, J. F. The permeability of rabbit leucocytes to sodium potassium and chloride. *J. Cell. & Comp. Physiol.*, 34: 493, 1949.
142. Wallace, G. B. and Brodie, B. B. The distribution of administered bromide in comparison with chloride and its relation to body fluids. *J. Pharmacol. & Exper. Therap.*, 65: 214, 1939.
143. Weir, E. G. and Hastings, A. B. The distribution of bromide and chloride in tissues and body fluids. *J. Biol. Chem.*, 129: 547, 1939.
144. Weir, E. G. Determination of the total chloride content of animals following administration of sodium bromide. *Am. J. Physiol.*, 127: 338, 1939.
145. Dunning, M. F., Steele, J. M. and Berger, E. Y. Measurement of total body chloride. *Proc. Soc. Exper. Biol. & Med.*, 77: 854, 1951.
146. Wallace, G. W. B. and Brodie, B. B. The distribution of iodide, thiocyanate, bromide and chloride in the central nervous system and spinal fluid. *J. Pharmacol. & Exper. Therap.*, 65: 220, 1939.
147. Gamble, J. L., Jr., Robertson, J. S., Hannigan, C. A., Foster, C. G. and Farr, L. E. Chloride, bromide, sodium and sucrose spaces in man. *J. Clin. Invest.*, 32: 483, 1953.
148. Threefoot, S. A., Burch, G. E. and Ray, C. T. Chloride space and total exchanging chloride in man measured with long-life radiochloride (Cl^{36}). *J. Lab. & Clin. Med.*, 42: 16, 1953.
149. Reid, A. F., Forbes, G. B., Bondurant, J. and Etheridge, J. Estimation of total body chloride by radiobromide dilution. *J. Lab. & Clin. Med.*, 48: 63, 1956.
150. Amberson, W. R., Nash, T. P., Mulder, A. G. and Binns, D. The relationship between tissue chloride and plasma chloride. *Am. J. Physiol.*, 122: 224, 1938.
151. Hiatt, E. P. Extreme hypochloremia in dogs induced by nitrate administration. *Am. J. Physiol.*, 129: 597, 1940.
152. Scatchard, G., Scheinberg, I. H. and Armstrong, S. H., Jr. Physical chemistry of protein solutions. IV. The combination of human serum albumin with chloride ion. *J. Am. Chem. Soc.*, 72: 535, 1950.
153. Gustavson, K. H. Some new aspects of the stability and reactivity of collagens. In: Connective Tissue, p. 185. Edited by Tunbridge, R. E., Keech, M., Delafresnaye, J. F. and Wood, G. C. Oxford, 1957. Blackwell Scientific Publications.
154. Hollander, F. Gastric secretion of electrolytes. *Fed. Proc.*, 11: 706, 1952.
155. Darrow, D. C., Harrison, H. E. and Taffel, M. Tissue electrolytes in adrenal insufficiency. *J. Biol. Chem.*, 130: 487, 1939.
156. Mudge, G. H. and Vislocky, K. Electrolyte changes in human striated muscle in acidosis and alkalosis. *J. Clin. Invest.*, 28: 482, 1949.

Seminar on Mycotic Infections

The Course and Prognosis of Histoplasmosis*

HARRY RUBIN, M.D., MICHAEL L. FURCOLOW, M.D., J. LEWIS YATES, M.D. *and*
Kansas City, Kansas *Mount Vernon, Missouri*

CHARLES A. BRASHER, M.D.
Mount Vernon, Missouri

PRIOR to 1935 histoplasmosis was diagnosed solely by the pathologist at postmortem examination [*1*]. Since then an increasing number of non-fatal cases have been described. In 1945 Christie and Peterson [*2*] first demonstrated that the distribution of histoplasmin sensitivity correlates closely with geographical areas having a high incidence of non-tuberculous pulmonary calcifications. Subsequent reports by these investigators [*3,4*] and others [*5–8*] have related histoplasmin skin sensitivity to pulmonary calcifications. Surveys of histoplasmin skin sensitivity in various parts of the United States [*9*] have shown that a benign form of histoplasmosis is quite common in certain endemic areas and, indeed, accounts for the overwhelming majority of all Histoplasma infections. On the basis of such data it has been estimated that there are thirty million people infected with H. capsulatum in the United States [*10*]. The spectrum of illness varies from asymptomatic infection with residual skin test sensitivity to disseminated fatal disease. The frequency of each clinical variety is not known although mild respiratory illness due to primary infection is probably common in the endemic area [*11*].

In 1948, the chronic pulmonary form of histoplasmosis was described by Bunnell and Furcolow [*12*] and Johnson and Batson [*13*]. Since then, this form of the disease has been reported more frequently. The majority of these cases have been found in tuberculosis sanatoriums [*14–18*]. One reason for the increased interest in this form of the disease is that chronic pulmonary histoplasmosis is clinically and radiographically indistinguishable from reinfection type pulmonary tuberculosis. The prevalence of chronic pulmonary histoplasmosis in tuberculosis sanatoriums in endemic areas has been estimated at 10 per cent on the basis of serologic surveys [*18*].

The present report is an analysis of this disease on the basis of 123 culturally proved cases of different clinical varieties, with follow-up studies in 90 per cent of them. With this large group of proved cases it is hoped that the clinical picture, course and prognosis of this disease can be more clearly deliniated.

METHODS

A review of the laboratory records at the Kansas City Field Station of the U. S. Public Health Service over the past twelve years revealed 123 culturally proved cases of histoplasmosis. All patients, except two, resided in areas highly endemic for histoplasmosis. This area in the mid-west is often referred to as the "Mississippi Valley." The patients were seen at this field station, at local hospitals in and around Kansas City, and in various tuberculosis sanatoriums in the endemic area. The majority of the patients from sanatoriums are from the Missouri State Sanatorium, where studies and serologic surveys for histoplasmosis were begun in 1950 [*18*].

Uniform data were collected from the records of the Kansas City Field Station and hospital charts. These data include information concerning fungus and acid-fast cultures, skin tests, serological tests, symptoms, physical findings and x-ray changes. All roentgenograms were reviewed by us.

Follow-up questionnaires were sent to all patients who were not available for personal interview. A statement of the present condition of the patient was elicited, and a recent chest roentgenogram, blood for serologic testing and sputum for fungus cultures were obtained whenever possible. Autopsy protocols were reviewed when available.

* From the Kansas City Field Station, Communicable Disease Center, Bureau of State Services, Public Health Service, U. S. Department of Health, Education, and Welfare, University of Kansas School of Medicine, Kansas City, Kansas, and the Missouri State Sanatorium, Mount Vernon, Missouri.

Intradermal skin tests were administered and read by the ward physician or by one of the physicians at the Kansas City Field Station. Purified protein derivative (PPD) in a dosage of 0.0001 mg. was employed in the tuberculin skin tests. The histoplasmin dosage used was 0.1 ml. of lot HKC-5 diluted 1 to 500, which is equivalent to other standard histoplasmins. The skin tests were read at forty-eight hours, and any reaction with 5 mm. or more of induration was considered positive.

The serums of all patients were studied for complement fixing antibodies using either histoplasmin or whole yeast phase organisms, or both, as antigen. These tests were made by Drs. Joseph Schubert and Kenneth Walls at the Communicable Disease Center, U. S. Public Health Service, Chamblee, Georgia. Complement fixation tests in a serum dilution of 1:8 or greater are considered serologically positive.

Cultures for fungi were performed in all cases. Mycologic studies were performed in the Mycology Laboratory at the Kansas City Field Station. Specimens from patients of the Missouri State Sanatorium were studied in the Mycology Laboratory at the Sanatorium. Specimens sent to the Kansas City Laboratory were mailed in sterile screw-capped sputum bottles to which penicillin and streptomycin (10,000 units of each per ml.) were added. Bacteriologic studies for tuberculosis, including smears, cultures and, in selected instances, guinea pig inoculations, were performed at the various hospitals and sanatoriums where the patients were hospitalized.

Tissue specimens obtained at autopsy or at surgery were examined in sections stained with hematoxylin and eosin as well as with special fungus stains, including the periodic acid-Schiff, Gridley and Grocott methenamine silver stains. Acid-fast stains were also performed. All sections were examined for typical intracellular yeasts of H. capsulatum and for acid-fast organisms.

RESULTS

The clinical classifications of the 123 cases are shown in Table 1. The number of follow-up examinations made in each clinical category is indicated in the table. Since acute pulmonary histoplasmosis is extremely difficult to distinguish from many other acute respiratory illnesses, very often the diagnosis is not made until late in the course of the illness when positive cultures are more difficult to obtain. A positive culture for H. capsulatum was a prerequisite for inclusion in this series, and the number of acute cases of pulmonary histoplasmosis in this analysis therefore was quite small. The results of the analyses will be presented under the different clinical headings.

Acute Pulmonary Histoplasmosis. Seven males and one female with culturally proved acute pulmonary histoplasmosis are included in this series. Their ages ranged from three to forty-nine years. These patients have been followed up from one month to twelve years, the average length of follow-up being three years. All eight patients are living and well.

TABLE 1
CLINICAL TYPES AND FOLLOW-UP STATUS OF 123 CULTURALLY PROVED CASES OF HISTOPLASMOSIS

Clinical Type	Total (no.)	No. with Follow-up	Per cent with Follow-up
Chronic pulmonary	90	78	87
Disseminated	25	25	100
Acute pulmonary	8	8	100
Totals	123	111	90

The initial cultural diagnoses were made from sputums in three cases, from gastric washings in three cases, and from pleural fluid and tonsil tissue in one case each. It is interesting to note that none of fifteen blood cultures and three bone marrow cultures from five patients was positive.

Results of histoplasmin skin tests were positive in six of eight patients. Only one patient had a positive reaction to the tuberculin skin test, and he also had a positive reaction to the histoplasmin skin test.

Results of complement fixation tests, using histoplasmin mycelial antigen, were positive during the acute illness in all these patients. The titers ranged from 1:8 to 1:64. In three patients results of serological tests were persistently positive for more than a year after the acute clinical episode had subsided. Complement fixation tests using whole yeast phase organisms as antigens were performed in two patients; in one the result was positive in a titer of 1:32, in the other it was negative.

The duration of clinical illness ranged from nineteen days to three months. Fever was present in all cases. The predominant symptoms were cough, chest pain, chills, sweats and dyspnea. Other less frequent complaints included fatigue, weight loss, hemoptysis (in three patients) and headache. Physical findings were scant. Three patients had pulmonary rales, one of these patients had a pleural effusion. Thrombophlebitis of the leg veins developed in two patients during their acute illness, one resulted in a pulmonary

TABLE II
AGE DISTRIBUTION OF TWENTY-FIVE PATIENTS WITH DISSEMINATED HISTOPLASMOSIS

Age (yr.)	No.
0–0.5	2
0.6–0.9	3
1–1.9	2
2–9	0
10–19	1
20–29	0
30–39	5
40–49	3
50–59	4
60–69	4
70–79	1
Total	25

TABLE III
SOURCE OF MATERIAL FOR INITIAL CULTURAL DIAGNOSIS IN TWENTY-FIVE DISSEMINATED CASES OF HISTOPLASMOSIS

Source	No.	Per cent
Blood	7	28
Sputum	5	20
Autopsy tissue	5	20
Biopsy tissue	3	12
Gastric washings	3	12
Bone marrow	1	4
Pleural fluid	1	4

embolism with infarction. Both patients made an uneventful recovery. White blood cell counts ranged between 8 and 14,000 cells per cu. mm. All hemoglobin determinations were within normal limits.

In seven patients chest roentgenograms showed diffuse nodular densities; in the eighth patient there was a localized pneumonic infiltration. Patients with diffuse nodular lesions demonstrable on chest films have been referred to as having the "epidemic type" of acute pulmonary histoplasmosis [*11*]. When a careful history is taken in cases of this type, additional illnesses in the family with a common source of exposure can usually be found [*19*]. Three cases in this series were found in association with small family epidemics, and in each of these three epidemics, H. capsulatum was isolated from the soil at a common source. Two patients with diffuse nodular lesions have shown complete clearing in roentgenograms taken eight months and two years after the initial examination. Two other patients have shown healing with diffuse nodular calcifications three or four years later. Two patients continue to show nodular densities after one month and a third patient after a year of follow-up; the densities appear more discrete. The roentgenogram of the patient with the localized pneumonic infiltrate showed complete resolution after eleven months and now shows a small calcification in the same area.

Disseminated Histoplasmosis. The twenty-five patients with culturally proved disseminated histoplasmosis ranged in age from less than six months to seventy-nine years. (Table II.) Five patients, or 20 per cent of the total group, are under one year of age and 48 per cent of the total number are over forty years of age. There are eighteen males and seven females, twenty-three of the patients are white and two are Negro.

Nineteen of the twenty-five patients died as a result of their disease, giving an over-all mortality of 76 per cent. The duration of these fatal illnesses ranged from one to thirty months, with an average duration of eight and a half months. Three of the six living patients were treated with amphotericin B and have been followed up for one month, one year, and one year, respectively. The remaining three were not given any "specific" treatment and are living and well after follow-up periods of seven, eight and eleven years.

The initial cultural diagnoses were made from autopsy tissue in five cases, or 20 per cent of the group. (Table III.) Three other cases were diagnosed initially by cultures of biopsy specimens of tissues obtained from oral, laryngeal and tongue ulcers during life. Blood was the most frequent source of culturally positive material from which the diagnosis was first made during life, next in order was sputum, then gastric washings.

The over-all frequencies of positive cultures from various clinical materials are shown in Table IV. The greatest percentage of positive cultures was obtained from bone marrow and tissue specimen, although these materials were not as frequently cultured as sputum, blood or gastric washings.

Fourteen of the twenty-five patients gave a positive reaction to the skin tests, eleven did not react to histoplasmin. This high percentage of negative reactions to the skin test possibly is a reflection of the clinical severity of the disease,

TABLE IV

OVER-ALL FREQUENCY OF POSITIVE CULTURES FROM VARIOUS CLINICAL MATERIALS IN TWENTY-FIVE DISSEMINATED CASES OF HISTOPLASMOSIS

Culture Material	Total No. Cultured	No. Positive	Per cent Positive
Bone marrow	15	11	73
Tissues	12	8	67
Sputum	82	35	43
Gastric washings	21	7	33
Blood	49	13	27
Pleural fluid	3	2	..
Spinal fluid	2	1	..
Abdominal fluid	1	1	..
Bronchial washings	3	0	..

TABLE V

FREQUENCY OF SYMPTOMS IN TWENTY-FOUR DISSEMINATED CASES OF HISTOPLASMOSIS *

Symptom	No.	Per cent
Fever	24	100
Weight loss	13	54
Cough	10	42
Chills	8	33
Fatigue	7	29
Weakness	6	25
Anorexia	6	25
Sweats	5	21
Dyspnea	4	17
Abdominal pain	4	17
Chest pain	3	12
Headaches	3	12
Vomiting	2	8
Diarrhea	2	8
Sore throat	2	8

* Symptoms unknown in one case.

with resulting anergy. The one patient with a positive reaction to the tuberculin skin test was culturally proved to have tuberculosis.

Results of complement fixation tests, using either histoplasmin or whole yeast phase organisms as antigens, were positive in fourteen (61 per cent) of the twenty-three patients in whom they were performed. The titers ranged from 1:8 to 1:512.

The most common symptoms in this group, and their frequency, are shown in Table v. Fever was present in all cases. Other symptoms, in order of frequency, were weight loss, cough, chills, fatigue, weakness and anorexia. A palpable liver and spleen were evident in seventeen patients, or 68 per cent. Abnormal breath sounds were noted in eight patients, five patients had lymph node enlargement, five had ulcerative lesions of the mucous membranes of the larynx, mouth and tongue.

White blood cell counts and hemoglobin determinations were within the normal range in more than half of the cases; however, seven patients had white cell counts of less than 4,000 cells per cu. mm. and nine patients had hemoglobin levels below 10 gm. per cent. Six patients showed both leukopenia and anemia. Data on platelet counts were not compiled.

Chest roentgenograms were normal in seven patients. Of the remaining eighteen patients, nine had diffuse nodular infiltrates in both lung fields, seven demonstrated discrete pneumonic infiltrations, and two had cavitary disease. Six patients with calcifications visible in their chest roentgenograms had negative reactions to tuberculin skin tests. In one patient with calcifications and cavitary disease, tubercle bacilli were isolated from the sputum; in none of the remaining five patients could tubercle bacilli be found.

Adrenal insufficiency in five patients developed, with repeated Addisonian crises. Of these, one patient is alive and maintained on 5 mg. of prednisone daily, the other four died and were autopsied; their adrenal glands were found to be completely necrotic. Other associated diseases included tuberculosis in two patients, and individual patients were found to have Hodgkin's disease, pulmonary torulosis, diabetes mellitus, leprosy, rheumatoid arthritis, bronchiectasis or thrombophlebitis.

Autopsies were performed in seventeen of the nineteen fatal cases. Table vi illustrates the frequency of involvement of various organs as shown by tissue staining or culture. As can be seen, the most frequently involved organs were lungs, adrenals, spleen, liver and lymph nodes. The brain was found to be involved in five of these disseminated cases.

Chronic Pulmonary Histoplasmosis. The ninety patients in this group were between twenty-six and seventy-nine years of age, with a median age in the fifty to fifty-nine year age group. Seventy per cent were fifty years of age or older. Ninety-two per cent were males and 8 per cent females; eighty-eight were white, two were Negro. Forty-four per cent of the entire group gave farming as their occupation. The length of follow-up

TABLE VI
FREQUENCY OF ORGAN INVOLVEMENT IN SEVENTEEN AUTOPSY CASES OF DISSEMINATED HISTOPLASMOSIS *

Organ	No. of Cases	Per cent of Cases
Lung	14	82
Adrenal	14	82
Spleen	14	82
Liver	12	71
Lymph nodes	12	71
Brain	5	29
Kidney	3	18
Intestines	3	18
Larynx	2	12
Esophagus	2	12
Heart	1	6
Tongue	1	6
Testes	1	6
Prostate	1	6

* Shown by either culture or microscopic section.

TABLE VII
FREQUENCY OF SYMPTOMS IN EIGHTY-NINE CASES OF CHRONIC PULMONARY HISTOPLASMOSIS *

Symptom	No.	Per cent
Cough	80	90
Weight loss	56	63
Dyspnea	47	53
Fever	47	53
Chest pain	41	46
Hemoptysis	40	45
Weakness	35	39
Fatigue	18	20
Sweats	16	18
Chills	12	13

* Symptoms not known in one case.

of these patients from the time of their first abnormal roentgenogram ranged from two months to twenty-six years; the average follow-up was forty months. Follow-up studies within six months preceding this analysis were obtained in seventy-eight patients (87 per cent).

The disease was fatal in sixteen of the ninety patients. Nine patients died as a result of their pulmonary disease, four following pulmonary surgery, two from myocardial infarction, and one from a bronchogenic carcinoma. The average duration of illness in the group of patients with fatal cases was sixty-nine months.

The initial cultural diagnosis was made from the sputum in seventy-nine cases, from lung tissue in seven cases (one obtained at autopsy and six obtained surgically), from bronchial washings in three cases and from gastric washings in one case. Four hundred and eighteen sputums, or 46 per cent of 902 cultured for fungi, were positive for H. capsulatum, and seventeen or 39 per cent of forty-four gastric washings were positive. The initial positive culture was obtained most often from sputum, since the majority of the patients raised copious quantities. In the few cases in which sputum was scant gastric washings were obtained. Six of nine bronchial washings were culturally positive, indicating such washings to be a good source of culture material.

Table VII shows the frequency of symptoms in the chronic pulmonary cases. The clinical picture, as indicated by the frequency distribution of symptoms, is that of a chronic pulmonary infection indistinguishable from any other, including tuberculosis. The most frequent physical findings included rales in thirty-eight patients, dullness to percussion in fourteen, and diminished breath sounds in thirteen. Except for weight loss in thirty-seven patients, no other abnormal physical findings were noted. Two patients with extensive pulmonary involvement were cyanotic and had clubbing of the fingers.

White blood cell counts were within the normal range in 59 per cent of the patients. Another 40 per cent had counts ranging between 10,000 and 20,000 cells per cu. mm. One patient had a white count above 20,000 per cu. mm. The differential counts were usually normal, as were the hemoglobin determinations. The erythrocyte sedimentation rates (Cutler method) were usually elevated, 93 per cent of seventy-six patients giving values above 10 mm. per hour. The median value was 25 mm. per hour, and the highest value was 49 mm. per hour.

Reactions to histoplasmin skin tests were negative in 20 per cent of these ninety culturally proved cases of chronic pulmonary histoplasmosis. Reactions to tuberculin skin tests were positive in 41 per cent and negative in 57 per cent of the group, with two results unknown. The reaction in eleven patients was negative to histoplasmin and tuberculin, another eight patients reacted positively to tuberculin but had a negative reaction to histoplasmin. These findings do not detract from the value of the histoplasmin skin test as a clinical and epidemiological tool but they do indicate that a

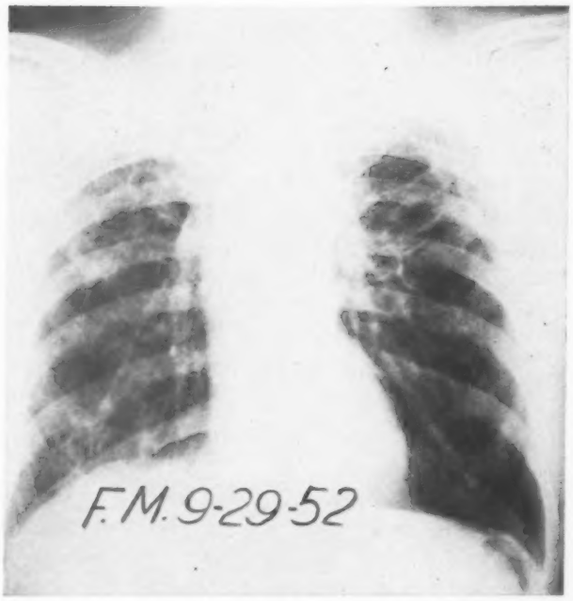


FIG. 1. A sixty-six year old white man with bilateral diffuse infiltrations, most marked in both upper lung fields, with highlights suggesting cavitation.

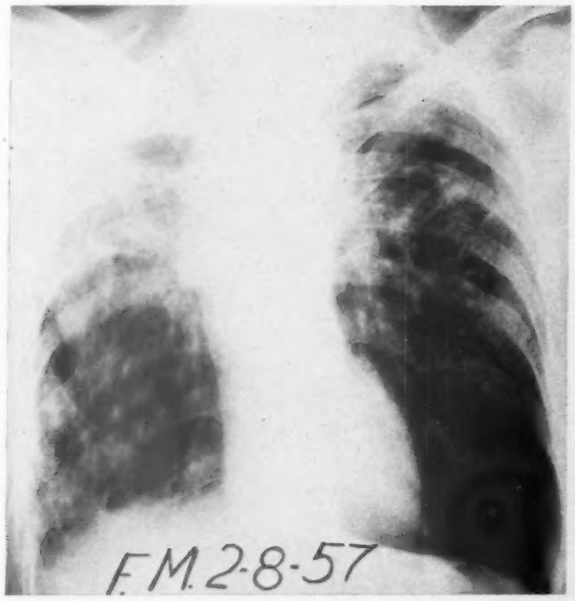


FIG. 2. Same patient five years later. There is now a marked increase in infiltration in the upper right lung field, with a large cystic cavity in the apex. The diaphragms are depressed and there is bilateral emphysema which is most marked on the left.

negative result of a skin test does not rule out the diagnosis.

Complement fixation tests were performed on serums from eighty-seven patients, using either histoplasmin or whole yeast-phase organisms as antigen. In most cases both complement fixation tests were performed. Seventy-nine patients, or 91 per cent of the total group, had titers of 1:8 or greater in either one or the other serological test, or in both tests. Only eight patients gave persistently negative serological reactions. The titers ranged from 1:8 to 1:1024 but most of the titers fell between 1:8 and 1:32.

Chest films revealed cavities in seventy-eight (87 per cent) of the ninety patients. Cavities were present in the apex or subapex of seventy-seven patients. One patient had a mid-lung cavity. Twenty-eight per cent of this cavitary group presented with bilateral cavities and 38 per cent had multiple cavities in the upper lobe.

Table VIII lists the six criteria which were used to evaluate progression by x-ray examination, and the frequency of each. Three patients were excluded from this analysis because only one roentgenogram of each was available for interpretation. Of the eighty-seven subjects analyzed, forty-three showed x-ray progression, forty-three had stationary lesions, and one showed improvement in the roentgenogram without specific treatment except bedrest and diet.

The percentage showing x-ray progression was directly proportional to the length of x-ray follow-up. Table IX illustrates this point. While only approximately 30 per cent of patients followed up for two years or less showed x-ray progression, 79 per cent of those followed up for three years or more demonstrated progressive lesions in serial chest roentgenograms. Figures 1 through 6 illustrate the progression of chronic cavitary histoplasmosis.

Acid-fast cultures were performed for the entire group; only five patients had less than three cultures each, the average number being seven. Twelve patients in the group had cul-

TABLE VIII
FREQUENCY OF CRITERIA FOR X-RAY PROGRESSION IN EIGHTY-SEVEN CASES OF CHRONIC PULMONARY HISTOPLASMOSIS

X-ray Criteria	No.	Per cent
New cavity formation	15	17
Spread to opposite lung	18	21
Spread to new area of same lung	16	18
Cavity enlargement	11	13
Bronchopleural fistula with empyema	2	2
Destruction of lung by cavities	2	2

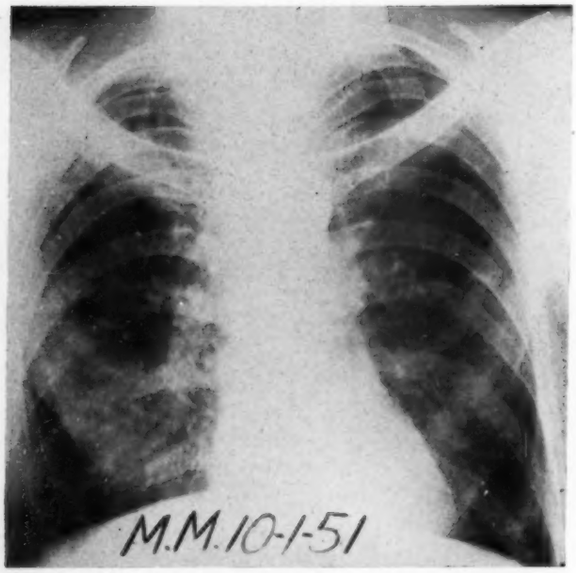


FIG. 3. A fifty-five year old white man with diffuse increase in pulmonary markings and evidence of pleural reaction in both mid-lung fields. There is some infiltration in the right subclavicular area.

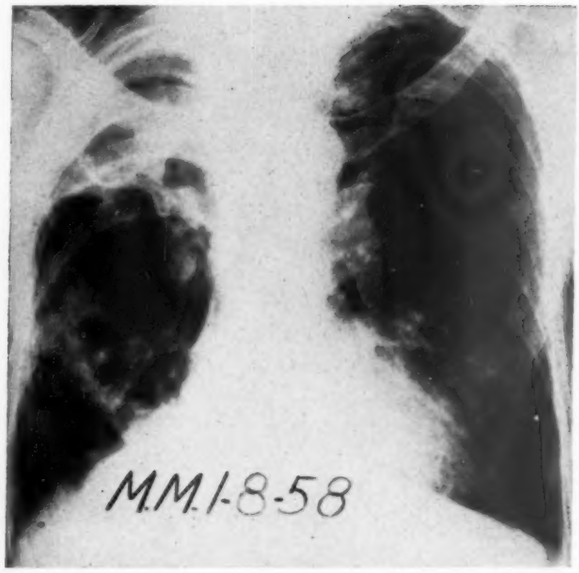


FIG. 4. Same patient six years later. There are extensive destructive changes in the upper right lung field, with multiple large cavities. There is also a severe degree of emphysema. (Figures 3 and 4 furnished through the courtesy of H. C. Darnall, M.D., Arkansas Tuberculosis Sanatorium, State Sanatorium, Arkansas.)

turally proved tuberculosis in addition to their infection with H. capsulatum.

Other pathological conditions, in addition to tuberculosis, were found in association with chronic pulmonary histoplasmosis. Bronchiectasis, demonstrated by bronchography or pathological study of the specimen, was found in seven patients. Six patients had pulmonary emphysema, and three had cor pulmonale and were in congestive failure. Six patients had arteriosclerotic heart disease.

Surgery was performed in nineteen of these patients. One had a two-stage thoracoplasty, and there were sixteen lobectomies and two pneumonectomies. Four of nineteen patients died one, three, five and ten days, respectively, after surgery. H. capsulatum was found by culture or tissue section in seventeen of the eighteen surgical lung specimens. Twelve of eighteen patients subjected to resectional surgery had complement fixation tests performed following surgery. Nine patients showed no change in titer when compared to the pre-surgery titer and three had a significant drop in titer, in two instances to zero.

TABLE IX
CHRONIC ACTIVE PULMONARY HISTOPLASMOSIS
X-RAY FOLLOW-UP OF EIGHTY-SEVEN CASES

X-ray Follow-up	Total No.	No. with Progression	Per cent with Progression
Less than 1 year...	27	8	30
1 to 2 years.....	27	9	33
3 years or more...	33	26	79
Totals.....	87	43	49

The present clinical status was elicited from sixty of the surviving seventy-four patients. Seventeen patients are asymptomatic, six are employed. The remaining forty-three are symptomatic. Only four of these are working. The most common complaints in this symptomatic group are productive cough, weight loss and dyspnea. Nine of these patients continue to show hemoptysis.

COMMENTS

Acute pulmonary histoplasmosis is almost invariably a benign infection, only rarely going on to more progressive disease. The present series contains eight such acute cases, however, seven of the acute "epidemic" variety. When we consider the pathogenesis of this acute type of infection, some pertinent prognostic observations emerge.

"Epidemic" cases are usually associated with a "point source" of infection, the most frequently described sources being unused chicken

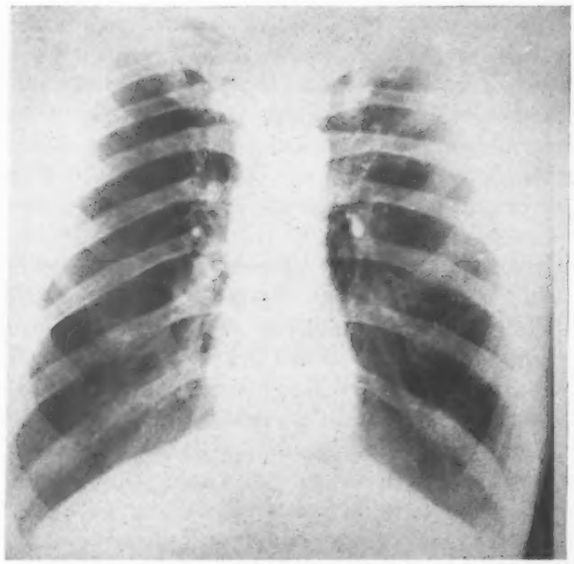


FIG. 5. A forty-nine year old white man with mottled infiltration in the left apex. Calcifications are evident in both hilar areas.

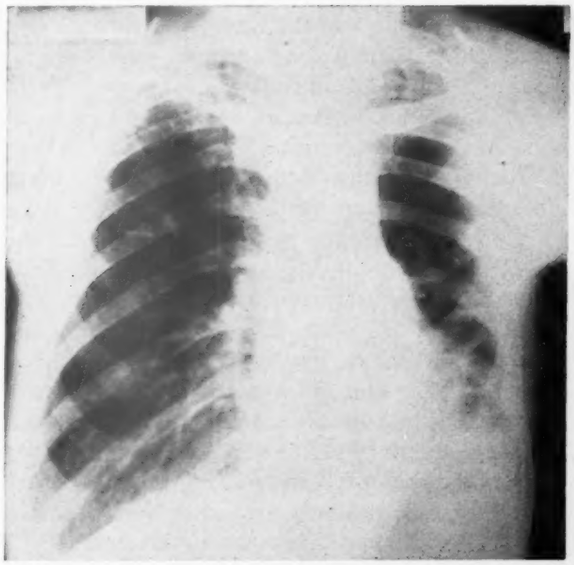


FIG. 6. The same patient six years later. A bronchopleural fistula has formed, with resulting collapse of the left lung, and there is empyema fluid at the left base. H. capsulatum was isolated from the fluid. In addition, infiltrations are now seen in the right apex, with probable cavitation in this area.

coops or caves, and damp shaded areas of soil. The clinical severity of this type of infection correlates well with the time and intensity of exposure to the "point source" [*20*]. The diffuse nodular infiltrations seen on the chest roentgenograms represent areas of the lung parenchyma where infectious chlamydospores of H. capsulatum have lodged, and the resultant inflammatory reaction. Seven of the eight cases of acute pulmonary histoplasmosis in this series were of this severe type, and all patients are alive after follow-up periods averaging three years. This small series, then, confirms previous observations concerning the usually benign course of this clinical type of Histoplasma infection.

The demonstration of calcifications in the liver and spleen of patients with inactive histoplasmosis [*21,22*] supports the concept of blood-borne dissemination at the time of the primary infection. The overwhelming majority of patients show no evidence of this primary dissemination beyond residual histoplasmin sensitivity and healed calcifications. One patient in this series illustrates this point quite well. This boy was three years old at the time of his acute infection, which was characterized by high spiking fever, cough, dyspnea and abdominal pain. His chest roentgenogram showed a miliary type of infiltration throughout both lung fields. His infection was accompanied by conversion of the result of his histoplasmin skin test to positive, together with a positive reaction to the complement fixation test. Recovery was uneventful in about one month. Sixteen months after his acute infection, a tonsillectomy was performed while the patient was asymptomatic, and H. capsulatum was isolated by culture of the tonsillar tissue. The patient is living and well twelve years later, and his chest x-ray film shows diffuse nodular calcifications in both lungs. Dissemination, occurring most likely during the primary infection, was proved by culture in this patient.

Disseminated cases of histoplasmosis were the first clinical type to be recognized, and since all the earliest cases described were fatal, it was assumed that this disease was uniformly fatal. Acutely progressive fatal cases continue to be recognized although at present insufficient data are available to estimate the actual incidence of this form of the disease. The twenty-five cases in this series all demonstrated clinical evidence of systemic dissemination to other organs. This evidence included hepatomegaly, splenomegaly, mucous membrane lesions or signs of adrenal insufficiency. The poor prognosis in this type of histoplasmosis is readily apparent, since only six of these patients survive at the present time; three were treated with prolonged courses of amphotericin B, the other three are alive after seven, eight and eleven years without

any form of specific therapy. The three latter patients had hepatosplenomegaly and anemia, and two also had leukopenia. It would seem then that not all clinically disseminated cases terminate fatally.

The organs most frequently involved, when dissemination from the lungs occurs, are those containing large numbers of reticuloendothelial cells. These include the spleen, liver and lymph nodes. Adrenal involvement is quite common, as was noted in this series, of which 20 per cent had Addison's disease. The clinicopathologic correlation in the four autopsy cases, with clinically evident adrenal insufficiency was striking.

Five patients of this group had mucous membrane lesions along with other signs of dissemination. All these patients were over forty years of age and all but one have died; this patient was treated with amphotericin B. The majority of reported patients with mucous membrane lesions are over forty years of age. The present experience and that quoted in the literature indicates that mucocutaneous lesions usually indicate disseminated disease. Occasionally, patients present with seemingly isolated mucocutaneous lesions without apparent active disease elsewhere. Such cases may have a prolonged course, however, and the prognosis in general is poor, as with all untreated disseminated cases.

The largest number of cases included in this analysis are of the chronic pulmonary variety. The majority of these ninety patients were hospitalized in a tuberculosis sanatorium at some time during the course of their illness, usually for prolonged periods of time. All were suspected of having chronic pulmonary tuberculosis on the basis of their clinical course and chest roentgenogram. Since it is only in recent years that chronic pulmonary histoplasmosis has been recognized as a distinct clinical entity, many of these patients spent years in sanatoriums despite the consistent absence of tubercle bacilli in their sputums. More than half of these patients also have negative reactions to tuberculin skin tests. Twelve per cent of these patients were proved to have concomitant pulmonary tuberculosis. Whether these acid-fast infections were acquired before or after admission to the sanatorium is a moot point. It is quite probable that some infections were acquired after admission since prolonged exposure in the sanatorium was not an uncommon occurrence.

The complement fixation test (as well as the histoplasmin skin test) has proved to be a valuable diagnostic tool in the chronic pulmonary variety of histoplasmosis. This has been especially true in tuberculosis sanatoriums situated in the endemic area where differentiation from chronic pulmonary tuberculosis is a paramount consideration. Serologic surveys performed in several of these sanatoriums [*23*] have been very valuable in this regard. In addition, serological tests serve as a useful guide in evaluating activity of the disease. That the titers are apt to be stable before and after surgery for localized lesions does not detract from the value of these serologic tests. Since primary blood-borne dissemination is quite common, it should not be concluded that a normal chest roentgenogram following surgery indicates absence of all infection. Viable organisms may be present in lymph nodes and other organs to account for persistent titers. Foci not visible on the routine chest film may also be present.

The development of bronchiectatic changes has been noted previously [*24,25*]. Bronchial obstruction has been implicated as a major factor in the pathogenesis of these changes [*26,27*]. When one considers the frequency of hilar lymphadenopathy in this infection, it would not be surprising to find some element of bronchial obstruction and subsequent bronchiectasis. Seven patients with chronic pulmonary histoplasmosis in this series were shown to have bronchiectasis.

Other findings worthy of mention include emphysema, found in six patients, and two patients with bronchopleural fistulas and empyema. Emphysema is not an uncommon finding and has been noted in previous reports [*28*]. Bronchopleural fistulas with empyema are apparently less common in histoplasmosis than in tuberculosis.

Some descriptions of this chronic pulmonary form of the disease have stressed its progressive nature [*18*]. Another [*29*] concluded that "the course is benign and is not altered by medical therapy." As a result, some controversy has arisen concerning whether or not this form of the disease is progressive. The present analysis, based on a large number of cases with an average follow-up period of forty months, clearly illustrates the progressive nature of this disease. Patients with chronic pulmonary histoplasmosis occasionally have clinical remissions and their chest roentgenogram may remain unchanged for months or years. However, when these patients are followed up for several years, the

majority show clinical and roentgenological progression to far advanced disease. While approximately 30 per cent of the patients showed progression in roentgenograms after two years of follow-up, the percentage showing progression after three or more years of follow-up rises very sharply, to 79 per cent in our series. In addition to showing x-ray progression, approximately three-fourths of these patients continue to be symptomatic. Their most common complaints consist of productive cough, weight loss and dyspnea. Nine patients continue to have occasional hemoptysis. Although these patients do not represent any public health hazard, treatment is indicated since the disease is far from benign and early diagnosis is as important as in tuberculosis. With the recent advances made in the therapy of the deep mycoses [*30,31*], these patients need not be consigned to a progressively debilitating downhill course. The use of amphotericin B should improve the prognosis of chronic pulmonary histoplasmosis.

SUMMARY

An analysis of 123 culturally proved cases of histoplasmosis is presented. The cases have been divided by clinical types and analyzed separately. Several pertinent observations concerning the prognosis of this infection emerge from the data:

(1) Acute pulmonary histoplasmosis is a benign infection in most instances. Although the number of such cases included in this compilation are small, they were all clinically severe and all patients are now in good health.

(2) Acute progressive histoplasmosis, often referred to as disseminated histoplasmosis, has a poor prognosis. There is clinical evidence of dissemination beyond the lungs to other organs. Included in this group are patients with seemingly isolated mucous membrane lesions. Such cases are usually fatal within one year although an occasional patient does survive.

(3) Chronic pulmonary histoplasmosis is characterized by cavities in the upper lobes. This form of the disease characteristically progresses gradually over several years, although remissions and exacerbations may occur. The prognosis is poor if the patients are not treated.

REFERENCES

1. Loosli, C. G. Histoplasmosis. *J. Chron. Dis.*, 5: 473, 1957.
2. Christie, A. and Peterson, J. C. Pulmonary calcification in negative reactors to tuberculin. *Am. J. Pub. Health*, 35: 1131, 1945.
3. Christie, A. and Peterson, J. C. Histoplasmin sensitivity. *J. Pediat.*, 29: 417, 1946.
4. Christie, A. Histoplasmosis and pulmonary calcification—geographic distribution. *Am. J. Trop. Med.*, 31: 742, 1951.
5. Palmer, C. E. Nontuberculous pulmonary calcification and sensitivity to histoplasmin. *Pub. Health Rep.*, 60: 513, 1945.
6. Palmer, C. E. Geographic differences in sensitivity to histoplasmin among student nurses. *Pub. Health Rep.*, 61: 475, 1946.
7. Edwards, L. B., Lewis, I. and Palmer, C. E. Studies of pulmonary findings and antigen sensitivity among student nurses; pulmonary infiltrates and mediastinal adenopathy observed among student nurses at the beginning of training. *Pub. Health Rep.*, 63: 1569, 1948.
8. Sontag, L. W. and Allen, J. E. Lung calcifications and histoplasmin-tuberculin skin sensitivity. *J. Pediat.*, 30: 657, 1947.
9. Manos, N. E., Ferebee, S. H. and Kerschbaum, W. F. Geographic variation in the prevalence of histoplasmin sensitivity. *Dis. Chest*, 29: 649, 1956.
10. Loosli, C. G. Histoplasmosis. Some clinical, epidemiological and laboratory aspects. *M. Clin. North America*, 39: 171, 1955.
11. Furcolow, M. L. The clinical diagnosis of histoplasmosis. *Postgrad. Med.*, 20: 349, 1956.
12. Bunnell, I. L. and Furcolow, M. L. A report on ten proven cases of histoplasmosis. *Pub. Health Rep.*, 63: 299, 1948.
13. Johnson, H. E. and Batson, R. Benign pulmonary histoplasmosis: a case report with brief review of literature. *Dis. Chest*, 14: 517, 1948.
14. Forsee, J. H., Puckett, T. F. and Hagman, F. E. Surgical considerations in focalized pulmonary histoplasmosis. *J. Thorac. Surg.*, 26: 131, 1953.
15. Peeples, W. J. and Spence, M. J. Pulmonary caviation due to histoplasma capsulatum. *Am. Rev. Tuberc.*, 69: 111, 1954.
16. Oliver, R. K., Holding, B. F., Jr., Henry, R. C. and Penton, S. Histoplasmosis; a roentgenographic survey of some Alabama counties: report of two cases with pulmonary cavitation. *J. M. A. Alabama*, 25: 113, 1954.
17. Post, G. W., Jackson, A. and Garber, P. E. Histoplasmosis on a small tuberculosis service in a general hospital. *Dis. Chest*, 31: 688, 1957.
18. Furcolow, M. L. and Brasher, C. A. Chronic progressive (cavitary) histoplasmosis as a problem in tuberculosis sanatoriums. *Am. Rev. Tuberc.*, 73: 609, 1956.
19. Lehan, P. H. and Furcolow, M. L. Epidemic histoplasmosis. *J. Chron. Dis.*, 5: 489, 1957.
20. Grayston, J. T. and Furcolow, M. L. Occurrence of histoplasmosis in epidemics: epidemiological studies. *Am. J. Pub. Health*, 43: 665, 1953.
21. Schwarz, J., Silverman, F. N., Adriano, S. M., Straub, M. and Levine, S. The relation of splenic calcification to histoplasmosis. *New England J. Med.*, 252: 887, 1955.
22. Serviansky, B. and Schwarz, J. The incidence of splenic calcifications in positive reactors to histo-

plasmin and tuberculin. *Am. J. Roentgenol.*, 76: 53, 1956.

23. Walls, K., Furcolow, M. L. and Lehan, P. H. Histoplasmosis as a problem in tuberculosis sanatoriums throughout the United States. *J. Lab. & Clin. Med.*, 51: 266, 1958.
24. Polk, J. W., Cubiles, J. A. and Buckingham, W. W. The surgical treatment of chronic progressive pulmonary histoplasmosis. *J. Thorac. Surg.*, 34: 323, 1957.
25. Baum, G. L. and Schwarz, J. Pulmonary histoplasmosis. *New England J. Med.*, 258: 677, 1958.
26. Croxatto, O. C. and Lanari, A. Pathogenesis of bronchiectasis: experimental study and anatomic findings. *J. Thorac. Surg.*, 27: 514, 1954.
27. Olson, D. E. Bronchiectasis. *Postgrad. Med.*, 18: 66, 1955.
28. Sutliff, W. D. Experience with the course and chemotherapy of chronic pulmonary histoplasmosis. *Am. Rev. Tuberc.*, 75: 912, 1957.
29. Sutliff, W. D., Hughes, F., Ulrich, E. and Burkett, L. L. Active chronic pulmonary histoplasmosis. *Arch. Int. Med.*, 92: 571, 1953.
30. Lehan, P. H., Yates, J. L., Brasher, C. A., Larsh, H. W. and Furcolow, M. L. Experiences with the therapy of sixty cases of deep mycotic infections. *Dis. Chest.*, 32: 597, 1957.
31. Procknow, J. J. and Loosli, C. G. Treatment of the deep mycoses. *Arch. Int. Med.*, 101: 765, 1958.

Clinicopathologic Conference

Hypertension, Renal Disease and Potassium Wasting

STENOGRAPHIC reports, edited by Lillian Recant, M.D., and W. Stanley Hartroft, M.D. of weekly clinicopathologic conferences held in the Barnes and Wohl Hospitals, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine, Preventive Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

A FORTY-THREE year old Negro housewife was admitted to the Barnes Hospital on October 6, 1958 with the chief complaint of high blood pressure.

With the exception of occasional frontal headaches, the patient had enjoyed apparent good health until ten months before her first admission to the Barnes Hospital. At that time the headaches were noted to have increased both in severity and duration and, in contrast to their previous character, were not relieved by the ingestion of Anacin.® Associated with the headaches were frequent episodes of lightheadedness, but never true vertigo. She was seen by a physician and admitted to a community hospital where she was told that she had high blood pressure. Following treatment with an unknown medication, she noted symptomatic improvement, lost 15 pounds, and was told that her blood pressure was normal. Following discharge she noted recurrence of headache when she neglected to take her medication, but otherwise did well until two months before admission here. At that time blurring of vision was first noted along with frequent episodes of dull non-radiating substernal burning pain aggravated by the supine position. Because of these symptoms she was referred to the Barnes Hospital for evaluation.

Mild exertional dyspnea had occurred at the onset of her present illness but subsided. In addition, some periorbital puffiness had been noted during the weeks prior to admission. No history of dyspnea, polyuria or renal infections was elicited although the patient had had nocturia (four to five times) for an indefinite period of time. Since the onset of the present illness the patient had lost 40 pounds.

Physical examination revealed the patient to be a well developed, well nourished Negro woman who was in no acute or chronic distress. The recorded vital signs were pulse, 96 per minute and regular; temperature, 37.2°C. (oral); respirations, 20 per minute; and blood pressure, 240/110 mm. Hg. A 2 by 2 by 2 cm. firm, movable, non-tender lymph node was palpated at the left posterior cervical triangle. There was a trace of pretibial edema. The scleras were injected, and examination of the optic fundi revealed marked arteriolar narrowing with prominent arteriovenous nicking. Several small punctuate hemorrhages were noted in both fundi. The neck was supple and the thyroid was not felt. The chest was symmetric with equal respiratory excursions. There were no abnormalities upon examination of the breasts, or upon percussion and auscultation of the chest. The cardiac point of maximal impulse was 14 cm. to the left of the mid-sternal line in the fifth intercostal space. The heart sounds were forceful, and the aortic second sound was substantially greater in intensity than the pulmonic second sound. A soft grade 2 (6 grades) blowing systolic murmur was heard over the entire precordium. The abdominal examination was within normal limits except for the presence of white striae at the lower lateral abdominal quadrants. The neurologic examination was also within normal limits.

Laboratory data on admission were as follows: hemoglobin, 11.6 gm. per 100 ml.; red blood cells, 3.76 million per cu. mm.; packed cell volume, 26 per cent; white blood cells, 7,700 per cu. mm. Differential: basophils, 2 per cent; segmented forms, 63 per cent; lymphocytes, 28 per cent; and monocytes, 7 per cent. There was

some anisocytosis of the red blood cells. Urinalysis revealed a specific gravity of 1.008; pH, 7.5; 3-plus proteinuria, and 5 to 6 epithelial cells. A full field of red blood cells was noted upon examination of the centrifuged specimen. Results of the stool examination and the serologic test for syphilis were both normal. Blood chemistry determinations were: non-protein nitrogen, 60 mg. per cent; fasting blood sugar, 97 mg. per cent; serum calcium, 8.6 mg. per cent; phosphorous, 2.7 mg. per cent; cephalin cholesterol flocculation test, negative; thymol turbidity, 1.4 units; total serum bilirubin, less than 0.8 mg. per cent; total serum proteins, 6.5 gm. per cent; albumin, 2.7 gm. per cent; and globulin, 2.8 gm. per cent. An L.E. preparation was negative. (See Table 1 for serum electrolyte studies throughout remainder of hospitalizations.) A phenolsulfonphtalein test revealed less than 5 per cent excretion of the dye at the end of fifteen and thirty minutes. A Regitine® test was negative. An electrocardiogram was interpreted as showing left ventricular enlargement, sinus tachycardia and questionable "P pulmonale." A repeat electrocardiogram taken twenty-one days later was unchanged. Roentgenographic examination of the chest was interpreted as demonstrating left ventricular enlargement, with widening and increased tortuosity of the aorta.

Following hospitalization the patient was noted to have an average systolic blood pressure of 220 to 230 mm. Hg., and an average diastolic blood pressure of 125 mm. Hg. Antihypertensive treatment, consisting of the administration of reserpine and hydralazine hydrochloride was initiated. On this regimen a substantial decline of blood pressure was noted to levels of 180 mm. Hg systolic, and 90 to 100 mm. Hg diastolic. Subsequentially she was maintained on these medications for the remainder of her life. Numerous urinalyses throughout this hospitalization were noted to have a specific gravity of not greater than 1.007, a constant 2- to 4-plus proteinuria, and microscopic pyuria and hematuria. Because of the consistent finding of white blood cells in the urinary sediment, frequently in clumps, several urine cultures were performed, all of which were negative for significant bacterial flora.

Midway through her hospitalization, and at the time of the decline in blood pressure, symptoms and signs of congestive heart failure developed which were associated with a rise in the non-protein nitrogen. She was digitalized and was given a low sodium diet, with good symptomatic response, and a decline in the non-protein nitrogen. Despite frequent episodes of emesis during the early part of hospitalization she improved symptomatically and subsequently was discharged on November 2, 1958, taking antihypertensive drugs and digitalis.

The patient was readmitted on November 14, 1958 for revaluation and treatment of congestive heart failure. During the interval twelve-day period, the patient had not followed her low sodium regimen, and exertional dyspnea and orthopnea developed, along with swelling of the ankles and a weight gain of 15 pounds.

Physical examination showed the patient to be lethargic and in moderate respiratory distress. Vital signs were: blood pressure 240/110 mm. Hg (sitting); temperature, 37°C. (oral); respirations, 20 per minute; and pulse, 85 per minute and regular. There were râles at both posterior lower lung fields. The cardiovascular examination was otherwise unchanged. The liver edge was palpated 7 cm. below the right costal margin at the mid-clavicular line. There was questionable ascites and 3-plus pitting edema of the ankles and legs.

Laboratory data on admission were: Hemoglobin, 8.9 gm. per cent; white blood cells, 5,100 per cu. mm.; with a normal differential. There was moderate hypochromia and anisocytosis of the erythrocytes. Urinalysis revealed a specific gravity of 1.008; reaction, 6.5; albumin, 2 plus; microscopic examination of the urine sediment was interpreted as showing 4 to 5 red blood cells, and a full field of white blood cells. Results of the stool examination and repeat serologic test for syphilis were negative. An electrocardiogram was interpreted as showing left ventricular enlargement, full atrioventricular conduction, and digitalis effect. Chest roentgenograms were interpreted as showing left ventricular enlargement, uremic pneumonia and cardiac failure. (For serum electrolyte determinations see Table 1.) Serum calcium was 9 mg. per cent; phosphorus, 4 mg. per cent; and cholesterol, 235 mg. per cent. Total serum proteins were 5.7 gm. per cent with albumin 3.5 gm. per cent, and globulin 2.2 gm. per cent. An L.E. preparation was negative. Urine culture was reported to have grown only a few colonies of Staphylococcus albus. A twenty-four hour urine aldosterone assay (specimen collected on previous admission) was reported to be 5.7 μg. (normal, 13 $\pm$ 3).

TABLE 1

SUMMARY OF LABORATORY DATA

	October										November			December
	2	5	8	10	12	13	17	18	22	28	1	6	15	1
Non-protein nitrogen (mg. %)	53	70	.....	.....	100	.....	....	54	62	.....	77	60	48	252
Fasting blood sugar (mg. %)	97	.....	.....	.....	....	.....	....	....	.....	.....	72	.....	....	76
Serum electrolytes														
Na (mEq./L.)	135	.....	130	.....	....	.....	....	139	138	135	135	.....	130	132
K (mEq./L.)	3.1	.....	2.9	4.3	....	.....	....	2.7	3.0	2.7	3.1	.....	3.2	5.2
Cl (mEq./L.)	76	75	.....	88	....	.....	....	108	.....	99	101	.....	90	94
CO_2 (combining capacity)	25	31.5	.....	27.3	....	.....	....	17.6	26.4	22.7	16.1	.....	25.8	9.7
Hemoglobin (gm. %)	11.6	10.1	.....	8.7	8.4	.....	....	....	.....	.....	.....	9.0	.....	5.2
Urine														
Na (mEq./L.)	.....	.....	.....	.....	....	19.5	....	31.7	27.8	.....	.....	.....	.....	.....
K (mEq./L.)	.....	.....	.....	.....	....	22.8	....	11.6	10.0	.....	.....	.....	.....	.....
Cl (mEq./L.)	.....	.....	.....	.....	....	31	....	30	25	.....	.....	.....	.....	.....
Volume (ml.)	.....	1100	.....	.....	....	1520	....	?	1590	.....	.....	.....	.....	.....
Blood pressure (mm. Hg)	220/125	200/120	190/100	180/100	180/95	180/100	210/95	210/95	200/100	210/110	230/110	225/110	240/120	210/90
Weight (lb.)	120	121	120	124	127	128	132	128	124	124	138	135	120	Not obtained

Therapy

Antihypertensive	October 10			
Digitalis		October 21		
Na+ restricted		October 21		
K+ restricted		October 22–October 28	K+ supplement and Diuril®	November 22

The patient was maintained initially on a regimen including the administration of antihypertensive drugs, digitalis, and sodium restriction. Her blood pressure remained essentially unchanged from that noted at the time of admission. Later therapy with chlorothiazide and supplemental oral potassium chloride was instituted and her weight decreased from 138 pounds to 121 pounds. The diuresis was attended by a marked symptomatic improvement and disappearance of ankle edema. She was discharged on November 30, 1958, taking antihypertensive medication, digitalis, low salt diet, potassium chloride and chlorothiazide.

The patient was admitted to the Barnes Hospital for the third time on December 18, 1958. She did not do well following discharge. She progressively lost weight and was unable to conduct her usual household duties. Edema of the ankles recurred and it was suspected that she was unable to adhere to a low salt diet. Several days before her final admission she became lethargic. On the day of admission the patient became inconsistent of urine and unresponsive.

Physical examination was as follows: The patient was a comatose, thin Negro woman with Kussmaul respirations. Blood pressure was 200/100 mm. Hg in both arms (with the patient in the supine position); pulse, 100 per minute and regular; temperature, 37.5°C. (rectal); and respirations, 20 per minute. There was diminished elasticity and poor turgor of the skin. Petechiae and purpura were present, especially notable over the anterior abdominal wall, and extending to a lesser extent to the distal extremities. There was marked pallor of the nail beds. Three plus pitting edema of the lower extremities and sacrum was present. Crusted blood was noted about the mouth. Upon examination of the optic fundi, numerous punctate hemorrhages were noted bilaterally in addition to numerous small soft white exudates. The disc margins were well defined. Retinal vascular changes previously noted were again observed. Nuchal rigidity was present. Many fine and coarse moist râles were heard upon auscultation of the posterior and posterolateral thorax. On examination, the heart was as before. The hepatic edge was palpated 10 cm. below the right costal margin. The deep tendon reflexes were noted to be decreased but symmetrical equal. No pathologic toe signs were noted.

Laboratory data on this admission were: Hemoglobin, 5.2 gm. per cent; red blood cells, 1.63 million per cu. mm.; white blood cells, 15,600 per cu. mm. Differential: basophils, 1 per cent; juvenile forms, 3 per cent; band forms, 4 per cent; segmented forms, 83 per cent; and lymphocytes, 9 per cent. Microscopic examination of the blood film was interpreted as showing toxic granulation of the segmented forms, and moderate to marked anisocytosis and poikilocytosis of the erythrocytes along with numerous hypochromic red blood cells. Urinalysis revealed a pH of 4.5, trace proteinuria, and 3 to 5 white blood cells per high power field were observed on examination of the sediment. Blood sugar was 76 mg. per cent and the prothrombin time was 42 per cent of normal.

A lumbar puncture at the time of admission revealed an initial pressure of 330 mm. water and a final pressure (after the removal of 10 ml. of spinal fluid) of 250 mm. water. The fluid was clear. There were no cells with acid and 14 cells without acid. Spinal fluid protein was 66 mg. per cent; sugar, 66 mg. per cent; and chloride, 119 mg. per cent. Colloidal gold was negative, as was the Wassermann test and culture. A nasopharyngeal culture revealed a moderate growth of Neisseria catarrhalis. Blood cultures were negative (reported postmortem).

The patient received vigorous therapy including the administration of parenteral fluids, antibiotics, and digitalis. Despite these measures she failed to respond and died quietly on December 19, 1958, fourteen hours after admission.

CLINICAL DISCUSSION

DR. SOL SHERRY: This was a forty-three year old Negro woman with probable onset of hypertension in January 1958 who died in uremia eleven months later. At the time of the supposed onset of her hypertension she was admitted to another hospital. The non-protein nitrogen on that admission was 25 mg. per cent and the urine findings revealed 1-plus proteinuria, some microscopic pyuria, a specific gravity of 1.008 and an acid urine. The patient was diagnosed as having essential hypertension, and there were no findings to suggest any other lesion. She was not seen at the Barnes Hospital until the last two months of her illness. The major features noted during her admissions to Barnes Hospital included severe hypertension responding poorly to therapy, proteinuria, microscopic hematuria, pyuria, rapidly progressive anemia and azotemia. Two months after she was first

seen, she was admitted for the third time with "uremic pneumonia," multiple petechiae and ecchymoses and died in coma. A roentgenogram of the chest taken on her first admission to Barnes Hospital revealed relatively normal lung fields; the sole abnormalities being left ventricular hypertrophy and some calcification in the arch of the aorta. Two months later, at the time of her last admission and shortly before her death, roentgenographic examination showed cardiac enlargement with extensive changes in the lung fields, particularly in the central areas, interpreted as a "uremic pneumonia" but often proving to be pulmonary edema. The interpretation of the electrocardiogram taken on this patient will be commented on by Dr. Massie.

DR. EDWARD MASSIE: There were three electrocardiograms. In essence they showed about the same findings, that is, evidence of left ventricular enlargement. By this diagnosis I do not mean to infer benign left ventricular enlargement; the T waves were quite inverted in the left ventricular leads and this could mean that there was relative ischemia of the left ventricular wall. The small R waves in leads V_1, V_2 and V_3 could have indicated the presence of an old anteroseptal infarction but this could occur in left ventricular enlargement without an infarction.

DR. SHERRY: Before embarking on a discussion on the diagnosis in this patient, two aspects raised by this patient's problem deserve further comment: (1) the hemorrhagic diathesis frequently observed in uremia and (2) the newer tests which may prove useful in interpreting the presence and nature of underlying renal disease. Recent studies suggest that a platelet thrombocytopathy commonly occurs in uremia. Dr. Sawyer, would you tell us about this?

DR. WILLIAM SAWYER: Dr. Lewis in 1956 studied twelve patients with uremia and hemorrhagic manifestations. In eight of the twelve patients studied, a striking feature was impaired prothrombin consumption which Dr. Lewis attributed to a thrombocytopathy. It is of interest that the blood urea nitrogen levels were strikingly elevated in all eight patients with this defect, the lowest being 78 mg. per cent. Dr. Johnson, in Detroit, has described similar findings, and described these as being cardinal signs of platelet factor 3 deficiency. Platelet factor 3 which has been tentatively identified as phosphatidyl serine, is a co-factor for thromboplastin formation and consequently an important constituent in the coagulation process. Dr. Johnson has recently studied a group of uremic patients and has demonstrated that their platelets were either markedly reduced or lacking in platelet factor 3 content. This acquired thrombocytopathy of uremia is to be differentiated from the congenital thrombocytopathies in which the platelets are adequate in their content of platelet factor 3, but for unknown reasons are unable to release it for participation in the clotting process. The exact significance and incidence of this platelet deficiency in uremia, and the therapeutic possibilities of administering platelet factor 3 still remain to be determined.

DR. SHERRY: We have recently learned that proteose determinations of the urine may be of value in distinguishing between inflammatory renal disease as contrasted to non-inflammatory renal disease. Dr. Kime, would you review this aspect for us?

DR. S. WESLEY KIME: Levin, Dubin, and Armstrong, have recently stated that in those cases of proteinuria which are associated with intrinsic renal disease results of proteose tests are positive. Thus positive reactions have been seen in chronic pyelonephritis, acute and chronic glomerulonephritis, the diabetic nephropathies and the nephritis of lupus erythematosus. However, positive reactions to proteose tests have not been noted in those cases in which intrinsic renal disease is not present. Thus the authors have not obtained positive reactions in congestive failure when proteinuria may be present.

DR. SHERRY: Do you believe that urinary proteose determinations would have been helpful in our patient?

DR. KIME: Perhaps it would have been helpful by indicating the presence of active intrinsic renal disease but certainly not helpful in defining the nature of that disease.

DR. SHERRY: Are there any other tests which might have been helpful in determining whether or not our patient had pyelonephritis?

DR. KIME: The urine cultures were negative, and this presents difficulties to those who would like to make the diagnosis of pyelonephritis. However, it should be pointed out that under some circumstances urine cultures may be negative in the presence of pyelonephritis. Of much less importance than urine cultures in the diagnosis of pyelonephritis is the finding of glitter cells, as noted by Sternheimer and others,

and pus cell casts in the urine. We do not consider glitter cells pathognomic of pyelonephritis, as some workers have suggested.

DR. SHERRY: Now let us turn to the diagnostic problem in this case. Dr. Perry, before considering the unusual features which relate to the electrolyte and acid base abnormalities, do you believe the patient was suffering from accelerated hypertensive disease?

DR. MITCHELL PERRY: No, everything considered, I do not. We tend to get lost in semantic problems and we ought to take just a moment to define what we mean by accelerated or malignant hypertension, since it means something entirely different to the pathologist and to the clinician. To the pathologist this means that there will be arteriolar necrosis, and this can only happen in the presence of azotemia. The clinician unfortunately is unable to say what the pathologist will find and to him the diagnosis of malignant hypertension merely means a very bad prognosis. On the average these patients will have died within eight months of the time that the diagnosis was made. The clinician usually insists on three criteria for diagnosis: (1) hemorrhagic and exudative retinitis with papilledema; (2) a diastolic pressure of at least 130 mm. Hg. and usually higher at hospital rest; and (3) evidence of renal dysfunction with proteinuria and decreased phenosulfonphthalein excretion or decreased clearances. The diagnostic problem here really lies between primary renal disease with hypertension and malignant hypertension which then goes on to involve the kidney. From a clinical point of view, this differentiation makes a great deal of difference since we can treat malignant hypertension, and lowering the blood pressure really benefits the patient. On the other hand, if there is underlying renal disease with some hypertension as a result, lowering the blood pressure does very little at all to help the patient. Now, my reasons for suspecting that this patient had underlying renal disease are several. As far as I can tell from the protocol, she did have long standing nocturia; at least it was of longer standing than her serious hypertension. Secondly, when she came into the hospital she had a diastolic pressure of 110 mm. Hg. Although the protocol finally says it averaged 125 mm. Hg, I suspect it was not high enough for malignant hypertension. Thirdly, there were no exudates or papilledema in the fundi. Finally, she responded quite well to what I would consider inadequate therapy for malignant hypertension. In favor of malignant hypertension are the following: she had hemorrhages in the fundi; her course went for a total of four months if we discount the one episode which apparently disappeared in January of the preceding year; she had a weight loss of 40 pounds which certainly is consistent with malignant hypertension; and she had hematuria.

DR. SHERRY: As I gather, you believe that considerable vascular disease will be found at autopsy but that there was something else present besides malignant hypertension *per se*.

DR. PERRY: Exactly.

DR. SHERRY: In approaching the problem of some underlying disease let us review the unusual features of this case: the patient had persistent hypokalemia and hypochloremia; relative systemic alkalosis in the face of azotemia; a urine specific gravity which was fixed at low levels; and a history of an abrupt onset of polyuria, particularly nocturnal in type. Dr. Morrin, would you agree that these findings suggest that our patient was suffering from a chronic hypokalemic state?

DR. PETER MORRIN: Yes, Dr. Sherry, I would agree with that.

DR. SHERRY: How does potassium deficiency produce these effects?

DR. MORRIN: It is now well recognized that hypokalemia can produce histological and biochemical lesions in the kidney. In man these involve mainly the convoluted tubules. The duration of hypokalemia in the reported cases was usually greater than one month. However, lesions have developed after seven days of hypokalemia. Functional and histological recovery can occur with potassium therapy but may take periods up to three months. Clinically polyuria, polydipsia, and muscular weakness are usually present. The urine is isosthenuric, acidic, and may contain protein. The urine potassium excretion is characteristically low unless there is some additional cause for urinary potassium loss. The serum potassium is low and the serum bicarbonate is elevated. The formation of an acid urine in the presence of an elevated serum bicarbonate is attributed to the fact that in hypokalemia the kidney excretes hydrogen ion in lieu of potassium. This leaves behind a bicarbonate ion which is paired with a reabsorbed sodium ion. There is also an increased reabsorption of bicarbonate.

DR. SHERRY: Although certain clinical evi-

dences are lacking, the laboratory findings, as previously noted, are strongly suggestive of a chronic hypokalemic state and raise considerations as to the mechanism of its production in our patient. There are four major mechanisms by which potassium depletion may occur: (1) a decreased intake or absorption from the gastrointestinal tract; (2) increased losses from the gastrointestinal tract; (3) increased urinary losses; and (4) an internal redistribution of potassium.

Decreased potassium intake alone usually does not lead to severe depletion, but it does become a major contributing factor when some other mechanism is also operative. Absorption from the gastrointestinal tract can be seriously interfered with in some of the malabsorption states; potassium deficiency has been described in idiopathic steatorrhea, in lymphosarcomatous involvement of the intestine, and in other states associated with a malabsorption syndrome. It is well recognized that severe potassium depletion can occur as a result of increased gastrointestinal losses and we are all familiar with the studies of Schwartz and his group on potassium depletion occurring in patients with chronic diarrheas induced by disease or through the use of laxatives. When increased renal losses of potassium occur, the condition is often referred to as a potassium losing nephropathy. The kaliuresis, under these circumstances, may be mediated by hormonal factors acting upon the kidney, or may result from the altered mechanisms of intrinsic renal disease itself. A transient internal redistribution or shifting of potassium from one compartment to another occurs in familial periodic paralysis, or after the administration of insulin, and may be associated with the symptoms and signs of potassium depletion.

Since, in our patient, there was no evidence of significant extra renal potassium loss but there was evidence of a significant potassium excretion with a high urinary potassium/sodium ratio at a time when the patient was hypokalemic, we may concentrate on states associated with a potassium losing nephropathy. Before considering these situations further, Dr. Bricker, would you tell us how the kidney normally handles potassium?

DR. NEAL S. BRICKER: Only a small fraction of the total body potassium is in the extracellular fluid and yet this quantity is extremely important to the well being of the organism. Its concentration must be carefully guarded, for deviations from normal in either direction may result in widespread abnormalities. The control of the concentration of extracellular fluid potassium depends largely upon (1) a dynamic equilibrium between the intracellular stores of potassium and the extracellular fluid potassium and (2) the kidney. The renal excretion of potassium must be integrated with the intermediary metabolic processes of the body relating to potassium as well as the dietary intake. There is an abundant amount of evidence to indicate that potassium is excreted in a rather unique manner by the kidney. It is filtered at the glomerulus and presumably is completely filterable. It is reabsorbed in the proximal tubule to a variable degree but perhaps in most situations rather completely. Finally, it is secreted into the tubular urine in the distal tubule. Extensive information now exists regarding the patterns of potassium secretion, however two points would seem to be of particular importance. First, there is increasing evidence that potassium is secreted in exchange for sodium ions in the intratubular urine. Second, the secretion of potassium is in some way interdependent upon the secretion of hydrogen ion and these two ions compete for the sodium in the lumen of the tubule. Although it is true that in certain instances there may be considerable amounts of potassium secreted into an acid urine, in general when one of the two ions appears in excess it is at the expense of the other.

DR. SHERRY: Other than in acute tubular necrosis, is it true that an increased kaliuria represents an increased secretion of potassium into the urine?

DR. BRICKER: Yes. In most forms of marked kaliuresis, increased tubular secretion appears to play a dominant role. However in the diuretic phase of acute tubular necrosis, postobstructive nephropathy and perhaps in experimentally induced osmotic diuresis, the urinary potassium may include increased quantities of unreabsorbed filtered potassium.

DR. SHERRY: What is known about hormonal factors influencing potassium secretion?

DR. BRICKER: It has been recognized for many years that in patients with Cushing's disease, potassium depletion may develop; and recently it has been noted by Conn and others that in aldosterone secreting tumors of the adrenal gland, potassium depletion typically occurs. It is now widely recognized and documented by experimental evidence that miner-

alocorticoids do indeed influence the renal excretion of potassium presumably by increasing the rate of secretion.

DR. SHERRY: Mudge* recently has reviewed the various types of potassium losing nephropathies or states associated with an abnormally high renal clearance of potassium sufficient to produce a negative potassium balance, and has classified these conditions into three groups: (1) those definitely not of renal origin, (2) those probably not of renal origin, and (3) those probably of renal origin.

Included among the extrarenal causes of kaliuresis are primary aldosteronism, Cushing's syndrome, patients receiving steroid therapy, the aldosteronism of edematous states, and metabolic alkalosis whether secondary to excessive alkali intake or following the vomiting of gastric contents. It may be noted that the potassium depletion seen in the latter situation does not occur simply from gastric losses but via renal losses induced by the developing alkalosis.

The potassium depletion observed following ureterosigmoidostomy is probably not of renal origin. Although renal dysfunction may contribute to the potassium depletion, recent evidence suggests a primary intestinal origin for the potassium disorder involving increased potassium secretion across the colonic mucosa. However, the kidney may become secondarily involved as a result of the potassium loss.

The potassium depletion states considered as probably being of renal origin include renal tubular acidosis, the Fanconi syndrome, acute renal insufficiency during the recovery phase and perhaps the postobstructive nephropathy as alluded to by Dr. Bricker. In renal tubular acidosis of the constitutional type in which the kidney appears unable to manufacture adequate amounts of hydrogen and ammonium ion, potassium substitution is usually invoked as the explanation for the kaliuresis.

The potassium losing states, seen in some cases of chronic renal insufficiency, in rare cases of nephrosis, and in a few instances of "potassium losing nephritis" which do not fall into any of the other categories, remain of questionable renal origin since the mechanisms for potassium loss in these latter conditions remain ill defined. In some patients with chronic renal disease, loss of base conserving mechanisms may result in potassium wasting, while in others a certain amount of sodium wasting may bring into play secondary adrenal factors which conserve sodium at the expense of potassium. In the few instances of "potassium losing nephritis" which cannot be categorized there appears to be an excessive secretion of potassium. We* made an extensive study of one such case in which it was possible to demonstrate excessive potassium excretion over a three-year period yet the features in this case were different from those described for hyperaldosteronism. Besides the features of the low potassium syndrome, the patient had postural hypotension, hyponatremia and a normal acid base balance. The patient had been maintained in good health for the past eleven years on oral potassium supplementation. Of interest is the recent report† of a potassium wasting state observed in two brothers; in one, autopsy did not reveal adrenal disease. One wonders whether or not some cases of "potassium losing nephritis" may be on a constitutional basis particularly since the patient we studied noted that his mother had similar recurrent episodes of muscle weakness.

The major differential diagnosis in the patient under discussion appears to be the following: (1) chronic renal disease with potassium wasting on the basis of renal mechanisms; (2) chronic renal disease complicated by aldosteronism by which I mean that the adrenals perhaps initially stimulated by salt wasting have become independently overactive in an autonomous manner resulting in a pattern of mixed renal disease and aldosteronism; or (3) primary aldosteronism complicated by accelerated hypertension which has led to renal failure. The presence of hypertension, a potassium losing nephropathy, nocturnal polyuria, and an alkaline urine instead of the paradoxical acid urine of potassium deficiency alone suggests that the patient had hyperaldosteronism. Dr. Eisenstein, does the low aldosterone assay exclude this possibility?

DR. ALBERT B. EISENSTEIN: No. In a number of reported cases of primary aldosteronism, it has been shown that the urine may contain normal or even decreased quantities of aldosterone. Hence, I can say that a single normal value for

* MUDGE, G. H. The kidney and potassium. *Bull. New York Acad. Med.*, 34: 152, 1958.

* EARLE, D. P., SHERRY, S., EICHNA, L. W. and CONAN, N. J. Low potassium syndrome due to defective renal tubular mechanisms for handling potassium. *Am. J. Med.*, 11: 283, 1951.

† FRANCE, R. and TOLLESON, W. J. Potassium depletion of undetermined origin in two brothers. *Tr. A. Climat. and Clin. A.*, 69: 106, 1957.

this urinary mineralocorticoid by no means rules out the diagnosis of primary aldosteronism. There is a very interesting case of Conn's disease studied by Simpson and Tait in England in which the only way it was possible to demonstrate a slight increase in aldosterone excretion was to pool the urine for several days before performing the assay.

DR. SHERRY: Are there any serious methodological problems in the aldosterone assay which may lead to errors?

DR. EISENSTEIN: There are many serious methodological problems in procedures used for determining aldosterone in biological fluids. In my opinion, there is only one reliable and reproducible method being used currently. This method was devised at the National Institutes of Health by Drs. Kliman and Peterson. The procedure involves labelling of isolated aldosterone with tritium after extraction from urine or plasma and in addition adding a known amount of C^{14}-labelled aldosterone so that recovery can be accurately determined. Since the manipulations concerned with aldosterone determinations are numerous and complicated, it is of great importance to know how much of the hormone is lost as it is carried through the procedure. Most other methods being used do not correct completely for losses of the hormone.

DR. SHERRY: In reviewing the literature, I have noted that when biological assays have been made in patients with primary aldosteronism, the results have almost invariably been positive. On the other hand, when chemical assays were performed, in a number of instances in patients with proved primary aldosteronism, the aldosterone assay was normal. Is it possible that there are other intermediates with biologic activity which are not being measured in the chemical assay?

DR. EISENSTEIN: I think that first one has to look at the methods that are used for biologic assay and for chemical assay. In most laboratories in which biologic assay for aldosterone is carried out, a crude extract of the urine is prepared and injected into the assay animal. The effect of this crude material on urinary sodium and potassium excretion is then determined. On the other hand, each of the various chemical methods used to measure aldosterone involved chromatographic steps. In some chemical procedures both column chromatography and paper chromatography are used to purify the extracts. Because there are so many additional steps necessary in the chemical analyses of aldosterone, the possibility of loss of the hormone is much greater than in the biologic assay. This may account, in part, for the lower values observed after such determination. Your suggestion that certain other substances are measured by the biologic assay that are not detected by chemical procedures is certainly possible but I have no information on this point.

DR. SHERRY: One other aspect of aldosterone assay concerns me; the assays are interpreted without consideration of the renal function. Our patient for example had considerable azotemia and renal insufficiency at the time the assay was performed. Is it possible that in such persons the urine assay does not necessarily reflect the serum activity?

DR. EISENSTEIN: It is certainly true, Dr. Sherry, that many of the urinary assays for aldosterone were performed on patients with this disorder when renal function was abnormal. My impression is that this does not interfere with the determination although I am not completely certain about this point.

DR. SHERRY: Do you believe our patient had hyperaldosteronium or not?

DR. EISENSTEIN: In answer to your question, I should like to quote the paper of Ayres et al. in which sixteen cases of primary aldosteronism were discussed.* Data concerning the average serum sodium, potassium and bicarbonate concentrations are presented. The serum sodium ranged from 141 to 156 mEq. per L. with a mean of 147.3 mEq. per L. In looking over the laboratory data on the patient being discussed, I noticed that there were few serum sodium values as high as 140 mEq. per L., most of the levels being between 130 and 140 mEq. per L. Marked potassium depletion occurred in the sixteen patients described by Ayres. The average serum potassium in this group was just slightly in excess of 2 mEq. per L. Our patient demonstrated mild to moderate potassium depletion with two or so determinations in the range of 2.7 or 2.8 mEq. per L. but most of the serum potassium levels were in excess of 3 mEq. per L. Furthermore, there was no good evidence of metabolic alkalosis in our patient since there was only one serum bicarbonate level of about 30 mEq. per L. whereas all of the others were within normal limits. The average serum bicarbonate in the sixteen cases of Ayres was 35 mEq. per L.

* AYRES, P. J., GARROD, O., TAIT, S. and TAIT, J. F. Aldosterone. p. 143. Boston, 1958. Little Brown & Co.

DR. SHERRY: It should be noted that the plasma bicarbonate in our patient was normal or increased in the face of definite azotemia, when some acidosis would have been anticipated

DR. EISENSTEIN: I certainly think this is an important point. I would summarize by saying that while the electrolyte abnormalities in our patient are suggestive of primary aldosteronism, they are not as marked as those that are generally found in this disorder. I do not think one can rule out this diagnosis with certainty but I do believe it is unlikely.

DR. SHERRY: Dr. Daughaday, do you agree with Dr. Eisenstein?

DR. WILLIAM H. DAUGHADAY: Particularly when the patient was alive our beliefs were the same as Dr. Eisenstein's. It is difficult to rule out the diagnosis of hyperaldosteronism. However, it seems a little unusual that alkalosis or some of the other manifestations that we associate with Conn's syndrome was not present at the time the patient had such marked hypertension.

I would differ a little with what Dr. Eisenstein had to say about the problem of aldosterone assay in renal insufficiency. The methods commonly employed measure free aldosterone and a labile conjugate which are probably influenced to a considerable extent by glomerular filtration. This is an argument in favor of not measuring free aldosterone, but the tetrahydroaldosterone derivative. A very interesting technic has been developed by Ulrick and his co-workers in New York at the Presbyterian Hospital in which they injected labelled aldosterone into patients and by an isotope dilution method calculated the total production of aldosterone. Normally, this averages out around 200 μg. per day. One of their patients whom they studied for a Conn syndrome was of great interest because by the chemical method, the aldosterone excretion in the urine from this patient was normal, but using the isotope dilution technic aldosterone excretion was of the order of 900 to 1,000 μg. a day. Particularly in the presence of renal insufficiency, the measurement of the tetrahydro derivative, with the isotope dilution method would be preferable.

DR. SHERRY: Dr. Bricker, very few patients with primary aldosteronism have died in renal failure; as a matter of fact, I know of none, although in some reported cases in which the patient was dying in renal failure the question has been raised as to whether or not primary aldosteronism existed. I am intrigued with the possibility that our patient had progressive chronic renal disease and then an element of aldosteronism developed. Would you go along with that view and if so what are your thoughts about the nature of the underlying renal disease?

DR. BRICKER: Historically there are two or three features in this patient that are disturbing in terms of fitting her course into the natural history of chronic Bright's disease. First, the onset of her illness was characterized apparently by hypertension and by concurrent polyuria, if we can extrapolate from nocturia to an increased total output of urine. Second, she had isosthenuria earlier than one would expect in the course of chronic Bright's disease and this persisted despite the presence of congestive heart failure. The third unusual feature is that the hypokalemia and relatively high bicarbonate concentrations persisted as the renal insufficiency advanced. One may indeed find hypokalemia in the patient with chronic Bright's disease, but in the majority of instances in which this has been described, replacement with potassium has resulted in restitution of the plasma potassium concentration to normal. This was not the case in this patient. For these reasons, it is our belief that there may well be something in addition to intrinsic renal disease. There undoubtedly is intrinsic renal disease, but one might explain this on the basis of increased aldosterone secretion leading to potassium depletion and hypokalemia nephropathy. One might then explain the progression of the lesion on the basis of the attendant hypertension and very likely, concomitant pyelonephritis.

DR. SHERRY: Of course, pyelonephritis must be seriously considered since the patient was a woman, had multiple pregnancies and died in uremia. The disturbing feature is that several urine cultures were sterile or nearly so. I do not believe we can go much further at this point and will summarize by expressing the view that the patient had chronic renal disease and hyperaldosteronism, and falls into that gray area in which either could have produced the other. Thus primary aldosteronism could lead to nephrosclerosis. On the other hand, electrolyte wasting in chronic renal disease could result in an abnormal adrenal response resulting in secondary aldosteronism.

The final clinical diagnoses are uremia secondary to chronic renal disease, nephrosclerosis, questionable chronic pyelonephritis; adrenal hyperplasia, or adenoma, questionable primary

or secondary; multiple petechiae and ecchymoses secondary to uremia; uremic pneumonia and hypertensive vascular disease.

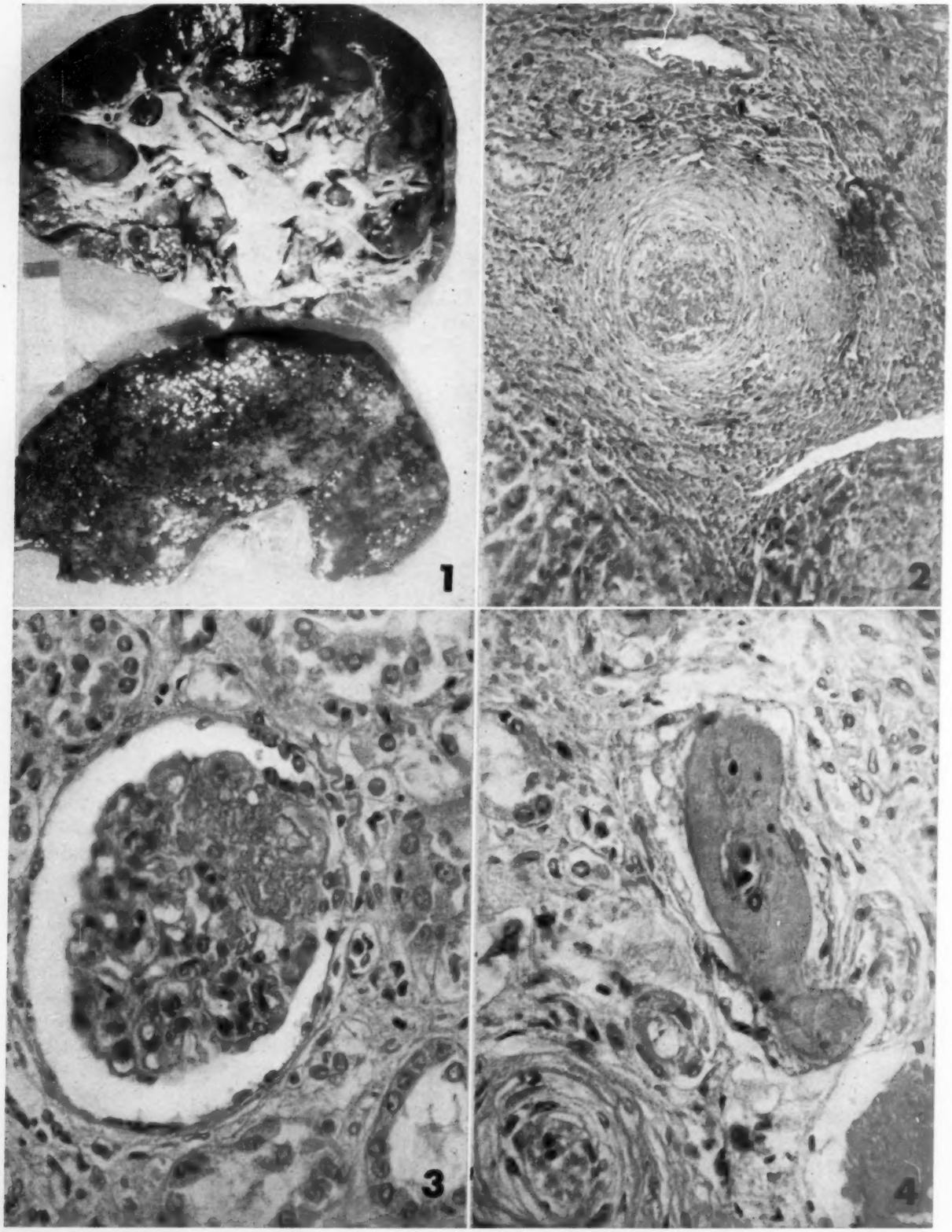
PATHOLOGIC DISCUSSION

DR. HIDESHIGE IMAI: On gross examination, the face, chest and arms of this Negro woman were covered with uremic frost. The kidneys were reduced in size, weighing 215 gm. The renal cortical surface was finely granular and the thickness of the cortex markedly reduced. (Fig. 1.) Arteries were prominent on the cut surface, indicating arteriosclerotic thickening of these vessels. Throughout the cortex, multiple petechiae were present, and ecchymotic areas were seen in the mucosa of the pelves. Gross lesions compatible with uremia were present in the lungs, pancreas, and alimentary tract. The lungs were diffusely congested and increased in weight. The pancreas showed dilatation of the larger ducts with inspissation of muddy secretion. The mucosa of the alimentary tract, especially of the small and large intestine, was edematous and congested; multiple mucosal hemorrhages were present. In the peritoneal cavity 50 ml. of serous fluid was present. The parathyroid glands were found very easily in their usual locations. They were symmetrically enlarged, weighing 250 mg. together. The color was light yellowish brown. The heart showed left ventricular hypertrophy and weighed 500 gm. In the right coronary artery multiple intimal hemorrhages were present. The right auricle contained a recent thrombus adhering to its wall; beneath the thrombus the myocardium was soft and hemorrhagic. In the left circumflex coronary artery multiple occluding, organized thrombi were found and there was a 2 by 5 cm. healed infarct on the lateral wall of the left ventricle. In the interventricular septum there were multiple scattered foci of fibrosis. The liver was of normal size but on cut surface the stumps of arteries were noted to be prominent and on close inspection thrombi could be seen filling the thick walled, smaller branches of the hepatic artery. Small hemorrhagic foci of necrosis of the parenchyma were seen throughout. In the central nervous system arteriosclerotic changes were advanced but multiple step sections revealed only a small, old infarct in the right dentate nucleus of the cerebellum. The spleen was moderately enlarged, soft and congested and all of the cervical, axillary, mediastinal and mesenteric lymph nodes were somewhat enlarged. Those in the region of the pulmonary hilus were enlarged, soft and contained focal areas of suppuration. The adrenals were enlarged, weighing 21 gm. together, and had thickened, nodular cortices of bright yellow. Multiple hemorrhagic foci of softening of the adrenal cortex were present and the periadrenal arteries contained occluding, organized thrombi. Vertebrae were not osteoporotic grossly and the marrow appeared normal.

DR. ROBERT O'NEAL: Older people often present a rather complicated picture at autopsy, with many disease states present; this patient was no exception. She did have advanced generalized arteriosclerosis with an old infarct of the heart and one of the right dentate nucleus of the cerebellum. These probably had no bearing on the current illness. A recent infarct of the wall of the right auricle underlay the mural thrombus seen grossly. This is an unusual site for an infarct, but it was small and also appears to have had no direct relation to her death.

The multiple, scattered thrombi that Dr. Imai described in the hepatic arteries and in the adrenal arteries were apparently complications of the advanced arteriosclerosis, the site of the thromboses being quite unusual. We found no source for systemic emboli and therefore assume the thrombi formed *in situ*. A very unusual complication of thrombosis of the hepatic arteries occurred in this patient—actual infarction of the parenchyma of the liver.* On Oil Red O stain, the borders of the infarcts were demarcated by fatty change in the surrounding viable liver cells. These were small infarcts, found only in relation to thrombi, and the liver parenchyma elsewhere was normal. The focal necroses in the adrenal cortex involved only a small part of the glands and probably were also the result of arterial thromboses. (Fig. 2.) The glomerular zone, which was easily identified and well demarcated, was of normal width. Throughout most of the cortex there was nodular cortical hyperplasia, not unusual in our autopsies but probably even less unusual in patients with hypertension. Lipid stains showed the nodules to contain large amounts of stainable fat in the adrenal cortical cells (incidentally, there was also considerable fat in one of the thrombi occluding an adrenal artery). Certainly nodular hyperplasia of the adrenal cortex is not really suggestive of "aldosteronsim," but is

* PARKER, R. G. F. Arterial infarction of the liver in man. *J. Path. Bact.*, 70: 521, 1955.



For descriptive legends to Figs. 1–4 see bottom of opposite page.

compatible with what we might find in that condition. But we also see nodular hyperplasia of the adrenal cortex similar to this in many patients who come to autopsy and so it is a rather non-specific finding.

The renal disease present was typical of arteriolar nephrosclerosis; we consider this the primary disease and principal cause of death. No evidence of pyelonephritis was seen. The small arteries were markedly arteriosclerotic, with very narrow lumens. Most of the glomeruli were fairly well preserved but many were hyalinized and occasional ones were partially "infarcted," portions of the glomerular tufts being necrotic. (Fig. 3.) Necrosis of arterioles were prominent, with nuclear fragments lying within hyaline arteriolar walls and vascular lumens were often no longer visible in these severely affected arterioles. (Fig. 4.) These morphologic changes were those that Dr. Perry expected us to find—those of arteriolar nephrosclerosis, malignant by morphologic criteria.

Changes typical of uremia were present in practically every organ. In the lung, hyaline membranes outlined many of the larger air spaces. (Fig. 5.) Some hemosiderin-filled macrophages were present, indicative of heart failure in the past. The fibrinous material in air spaces and the hyaline membranes were found in many areas, but only a few focal areas of bronchopneumonia were present. In the pancreas, as Dr. Imai described grossly, the ducts were dilated and filled with inspissated secretions. This is probably a result of dehydration more than of uremia *per se*. The inspissated secretions were associated with small areas of recent pancreatic necrosis. (Fig. 6.) The parathyroids provided a good example of the changes of early hyperplasia of the parathyroids. Chief cells were packed with monotonous uniformity throughout the glands, with only an occasional fat cell present. In a woman of this age there should be a great deal more fat than this. In a few areas the cells were larger, with clear cytoplasm and eccentrically placed nuclei. In the heart there was marked fatty change in the myocardial fibers, probably the result of severe anemia. The bone marrow was markedly hyperplastic with striking erythroid hyperplasia, practically no fat remaining in vertebral bone marrow. (Fig. 7.) A great deal of extramedullary hematopoiesis was present in the liver, little clumps of erythropoietic cells scattered throughout the liver, as much as I have seen in an adult. (Fig. 8.) In uremia we usually expect, in an anemic patient, to see hypoplastic bone marrow, sometimes the hemapoietic tissue being practically gone, but here it was extremely hyperplastic. However, there was no evidence of a primary disease of the bone marrow.

As I said in the beginning, autopsy findings can be difficult to interpret because patients, especially older ones, seem prone to have multiple disease processes. The one in this patient that gave us our biggest surprise was blastomycosis of the mediastinal lymph nodes. The mediastinal nodes, that Dr. Imai noted grossly had areas of necrosis, microscopically contained numerous organisms to which there was a well developed granulomatous reaction. (Fig. 9.) Like the arteriosclerosis, this does not appear to have played a significant role in the patient's death.

The final anatomic diagnoses are arteriolar nephrosclerosis, advanced, with widespread necrosis of arterioles (anatomically "malignant"); hyaline arteriolosclerosis, advanced, generalized; "uremic pneumonitis" with hyaline membrane formation; dilatation of pancreatic ducts and acini with inspissated secretion; secondary hyperplasia of parathyroids (250 mg.); hypertrophy of the heart; erythroid hyperplasia of the bone marrow and extramedullary hematopoiesis in the spleen and liver. Arteriosclerosis, generalized, advanced; healed myocardial infarct of lateral wall of left ventricle; small healed infarct of the right dentate nucleus; recent infarct of the right atrium with recent overlying mural thrombus; recent thrombi in branches of the hepatic and adrenal artery with

---

FIG. 1. Gross photograph of a kidney showing the marked granularity of the cortical surface and many dark petechiae.

FIG. 2. A recent, organizing thrombus in a periadrenal artery, typical also of those found in small hepatic arteries. Hematoxylin and eosin × 100.

FIG. 3. A partially necrotic glomerulus, typical of the many "lobular infarcts" found in the kidneys. Nuclei have completely disappeared from the necrotic area. Hematoxylin and eosin × 420.

FIG. 4. Renal arteriole with necrotic, hyalinized wall, the characteristic morphologic change of malignant arteriolar nephrosclerosis. The small artery in a corner of the photomicrograph has loose, laminated intimal fibrous tissue markedly narrowing its lumen. Hematoxylin and eosin × 420.

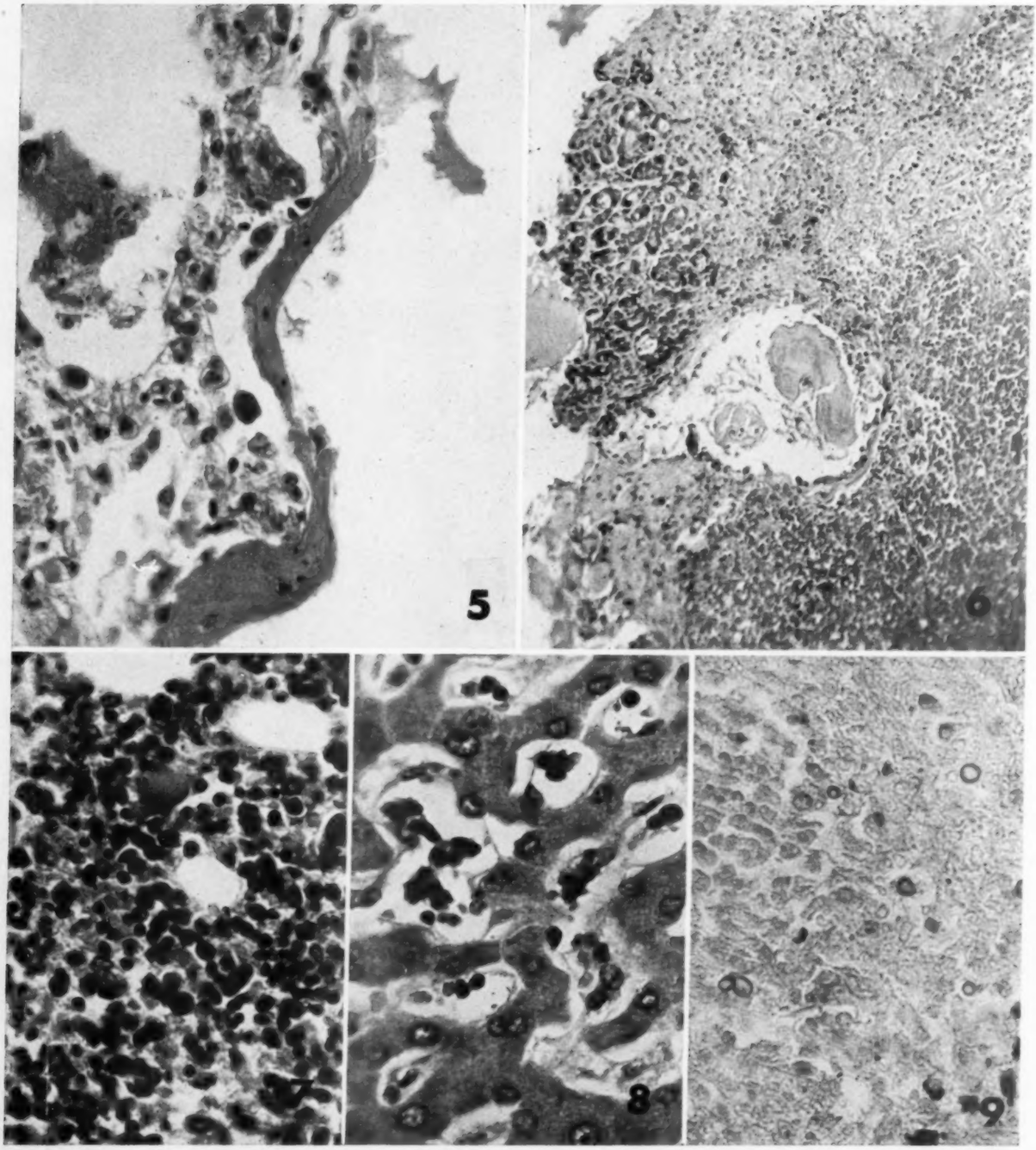


FIG. 5. A dense hyaline membrane overlying the wall of an air space in the lung. This is one of the typical findings in fibrinous ("uremic") pneumonitis. Hematoxylin and eosin × 420.

FIG. 6. This small pancreatic duct contains inspissated secretions and a large, pale area is present in the pancreatic parenchyma. A marked neutrophilic reaction was present about many of the necrotic areas, indicating that this was more than an agonal process. Hematoxylin and eosin × 100.

FIG. 7. Vertebral bone marrow. Marked hyperplasia, especially of erythropoietic elements, has reduced the amount of fat remarkably. Hematoxylin and eosin × 420.

FIG. 8. Foci of erythropoiesis in the hepatic sinusoids. All the small dark cells, lying in clumps and pairs, are immature forms of red blood cells. Hematoxylin and eosin × 420.

FIG. 9. Budding forms of blastomyces in a mediastinal lymph node, appearing as rounded, smoothly contoured bodies with dark walls. Periodic acid—Schaff stain × 420.

recent infarcts in both adrenals and the liver; organized thrombi in the inferior vesical arteries, bilateral. Blastomycosis in mediastinal lymph nodes. Focal bronchopneumonia; adrenal cortical hyperplasia, moderate (combined weight 21 gm.).

DISCUSSION

DR. SHERRY: Dr. Lang, would you comment on the bone marrow findings?

DR. ROBERT LANG: In uremia, the bone marrow findings can be extremely diverse with hyperplastic marrows observed in some cases, normal cellularity in others and hypoplastic marrows in still others. In this particular patient there was evidence of either marked blood loss or hemolysis during the last few weeks of her life and this probably led to a marked erythroid hyperplasia in a bone marrow still able to respond by formation of increased numbers of red cells.

DR. BRICKER: Dr. Sherry, I think it is important to try to get a little closer to the answer because if this patient did have primary aldosteronism associated with bilateral adrenal hyperplasia, it would be perhaps the first case reported in an adult woman. In this regard, I would like to ask if any meaningful assay procedures on the adrenal glands might still be performed and secondly, I would like to ask Dr. O'Neal if it is not unusual for a patient with a chronic progressing renal disease to die, having lost 40 or more pounds, and yet have hyperplastic adrenal glands.

DR. O'NEAL: Actually we would expect the patient to have lipid depleted adrenals. As you know, we commonly describe lipid depletion of the adrenals at these conferences. However, in a patient with nodular hyperplasia the lipid content of these nodules is usually retained, as it was in this patient. Unfortunately, adrenal tissue from this patient is no longer available.

DR. SEYMOUR REICHLIN: There were two unusual findings in this patient: adrenal hyperplasia and an infarct of the right atrium. Although the temporal relations in this case do not support an association, it is conceivable that disturbed adrenal function may be caused by right atrial damage. Anderson et al.* have recently shown that there are stretch receptors in the right atrium which control aldosterone output. Distention of the right atrium inhibits secretion of this steroid; an infarct could thus reduce the inhibitory impulse arising from the atrium in a manner analogous to the chronic hypertension that follows denervation of the carotid sinus.

DR. ERIC REISS: Dr. Sherry, would you have recommended an adrenalectomy earlier in this patient's course?

DR. SHERRY: Perhaps as Dr. Reiss suggests, an adrenalectomy should have been recommended for this patient but unfortunately the low aldosterone assay confused the issue.

Before moderating the discussion, I had the feeling that the pathologist might not be able to settle the question as to the relation of the adrenals to the hypertension, renal disease and potassium wasting in this patient, and you will agree they have not. Our case is not too dissimilar to cases previously reported by others† in which hypertension, renal disease and potassium wasting coexisted and in which the part played by the adrenals is unclear. Perhaps further studies on similar cases may unravel this problem but until that time we should recognize that there may be a gray area in which it may be difficult to distinguish between potassium wasting in chronic renal disease *per se*, or in association with primary or secondary aldosteronism.

* ANDERSON, C. H., MCCALLY, M. and FARRELL, G. L. The effects of atrial stretch on aldosterone secretion. *Endocrinology*, 64: 202, 1959.

† SYNGAARDEN, J. B., KEITEL, H. G. and ISSELBACHER, K. Potassium depletion and alkalosis. Their association with hypertension and renal insufficiency. *New England J. Med.*, 250: 597, 1954.

† BROOKS, R. V., MCSURNEY, R. R., PRUNTY, F. T. G. and WOOD, F. J. Y. Potassium deficiency of renal and adrenal origin. *Am. J. Med.*, 23: 391, 1957.

Research Society Abstracts

Southern Society for Clinical Research

ABSTRACTS OF PAPERS PRESENTED AT THE THIRTEENTH ANNUAL MEETING, NEW ORLEANS, LOUISIANA, JANUARY 23, 1959

A STUDY OF LONG TERM ADMINISTRATION OF INTRAVENOUS FAT IN PATIENTS. *Curtis P. Artz,* J. Harold Conn and Warren N. Bell.* Dept. of Surgery and Div. of Hematology, Univ. of Mississippi School of Medicine, and the V. A. Center, Jackson, Miss.

A safe and effective intravenous fat emulsion has recently been released for general use. Jaundice and spontaneous hemorrhage have been seen after the long-term administration of large quantities of this emulsion. This study was designed to ascertain the effects of prolonged administration of large quantities of this intravenous fat emulsion in patients by carrying out liver function tests and coagulograms at regular intervals during therapy. Twenty-two patients received 10 or more units of intravenous fat emulsion, totaling 481 units to the group. Eleven of the patients received 14 or more units and a study of these patients forms the basis of this report. In all patients there was a fall in hematocrit and increased retention of bromsulfalein. Clinical jaundice was present in two patients but disappeared after cessation of therapy. The prothrombin time was prolonged in six patients and the coagulation time prolonged in five. In seven patients the prothrombin consumption time was diminished. Other liver function and coagulation studies were not significant. Three patients who received 17, 32 and 42 units, respectively, experienced bleeding episodes which ceased after therapy was discontinued.

It is suggested that treatment with 10 to 14 units of intravenous fat emulsion is safe. Should further therapy be necessary, liver function tests and coagulograms should be carried out at regular intervals.

FURTHER OBSERVATIONS ON THE ACETYLCHOLINESTERASE ENZYME IN PNH ERYTHROCYTES. *Joseph V. Auditore and Robert C. Hartmann.** Dept. of Medicine, Vanderbilt Univ. School of Medicine, Nashville, Tenn.

Erythrocyte acetylcholinesterase was strikingly and consistently reduced in eight cases of paroxysmal nocturnal hemoglobinuria (PNH). A preliminary survey of patients with other miscellaneous blood dyscrasias revealed no marked alteration in the activity of the enzyme.

Cholinesterase deficiency was present in young as well as mature PNH cells. Stroma prepared from PNH erythrocytes showed reduced enzyme activity. Low acetylcholinesterase activity did not develop in normal cells transfused into patients with PNH.

The reduced enzyme activity could not be activated by the oxime, 2-PAM. *In vitro* mixing of normal and PNH erythrocytes did not alter the activity of the abnormal cells. No changes in red cell enzyme activity were found on mixing normal serum with PNH erythrocytes and normal erythrocytes with PNH serum. "Artificial" PNH erythrocytes could not be produced by treating normal cells with certain cholinesterase inhibitors. Since acetylcholinesterase may play a part in regulating cellular membrane pH, the susceptibility of PNH erythrocytes to hemolysis in *acidified* serum may be related to the deficient cholinesterase activity.

PROTECTION AGAINST STRANGULATION OBSTRUCTION FLUID BY IMMUNIZATION. *William O. Barnett and M. Don Turner.* Dept. of Surgery, Univ. Medical Center, Jackson, Miss.

Peritoneal fluid resulting from strangulation obstruction of the ileum is lethal when injected into the peritoneal cavities of normal dogs. The purpose of this study was to determine if immunity against a lethal dose of this fluid could be developed.

Group 1. Ten dogs served as donors for peritoneal fluid following strangulation of the lower ileum.

* The asterisk designates members of the Southern Society for Clinical Research.

Group 2. Five normal dogs received an intraperitoneal injection of strangulation fluid (3 cc./kg.). All were dead within twenty-four hours.

Group 3. Ten animals were given three intraperitoneal injections each of strangulation obstruction fluid (.2 cc./kg.) at weekly intervals. They were then given an intraperitoneal injection of toxic fluid in the amount of 3 cc./kg. Eight of these animals recovered.

Group 4. Five animals were immunized as in group three except that they were given 600,000 units of penicillin at the time of each weekly injection. One week after the last immunization an intraperitoneal injection of toxic fluid in the amount of 3 cc./kg. was given. All animals recovered.

Group 5. Five animals were given three intravenous injections of strangulation fluid (.2 cc./kg.) at weekly intervals. They were then given an intraperitoneal injection of toxic fluid (3 cc./kg.) and three animals recovered.

It is concluded that it is possible to immunize normal dogs against an otherwise lethal dose of toxic strangulation obstruction fluid. The immunizing dose may be given via the peritoneal or venous route. Moreover, the simultaneous administration of penicillin does not interfere with the development of immunity.

TUBERCULOUS GLOMERULONEPHRITIS. *Leonard B. Berman, Tatiana Antonovytch and James Duke.* Dept. of Medicine and Pathology, Georgetown Univ., and Georgetown Div., D. C. General Hospital, Washington, D. C.

Previous studies of the renal lesions of tuberculosis, in tissue removed at autopsy or during surgery, have uniformly been reported to reveal a negligible incidence of glomerulonephritis. The present investigation records the results of percutaneous biopsy of the kidney in twelve patients with proved pulmonary tuberculosis. The clinical diagnoses included renal tuberculosis in three patients, acute glomerulonephritis in one patient, and normal kidneys in eight patients.

All twelve biopsy specimens showed acute, diffuse glomerulonephritis ranging from mild to severe. Glomerular changes included hypercellularity, polymorphonuclear leukocyte infiltration, thickening of the basement membrane, crescent formation, obliteration of capillary loops and glomerular enlargement. Cortical tubercles with acid-fast organisms were seen in two biopsy specimens.

The pathogenesis of the glomerular lesions is not clear. Experimentally, glomerulonephritis has been produced in tuberculous pigs by the injection of tuberculin into a renal artery. The human subjects may be exhibiting a similar phenomenon, i.e., glomerular hypersensitivity to tuberculous products in tuberculous subjects. The possibility is supported by the variety of hypersensitivity lesions seen in tuberculosis, as well as the experimental production of glomerulonephritis by diverse antigens.

HYPOCHOLESTEROLEMIC EFFECTS OF β-SITOSTEROL AND NICOTINIC ACID. *Maurice M. Best,* and Charles H. Duncan.* Dept. of Medicine, Univ. of Louisville School of Medicine, Louisville, Ky.

β-Sitosterol (18 gm./day) and nicotinic acid (6 gm./day) have been administered singly and in combination to a group of patients with elevated serum cholesterol levels for periods of time ranging from 10 to 168 weeks. Six patients were selected from a larger group treated with β-sitosterol alone, on the basis of their less than usual hypocholesterolemic response.

Four patients with arteriosclerotic heart disease had a mean pretreatment serum cholesterol of 286 mg./100 ml. (264 to 335 mg./100 ml.). Administration of β-sitosterol resulted in a mean reduction of 8.6 per cent (5 to 12 per cent); administration of nicotinic acid alone exerted a similar effect, the mean reduction being 8.8 per cent (2 to 19 per cent). When administered in combination for a period of twenty weeks the two drugs had an additive effect, the mean cholesterol being 238 mg./100 ml. (16.3 per cent mean reduction).

Two patients with hyperlipemic hypercholesterolemia appeared to be unusually responsive to the administration of nicotinic acid. A reduction of cholesterol from the pretreatment mean of 565 to 294 mg./100 ml. was observed.

Side effects were encountered only during periods of nicotinic acid therapy, the gastrointestinal symptoms, flushing and pruritus making prolonged administration difficult.

TUBULAR REABSORPTION OF SODIUM AND CHLORIDE. *E. H. Bresler.* Dept. of Medicine, Tulane Univ. School of Medicine, and V. A. Hospital, New Orleans, La.

According to current theory, renal tubular reabsorption of water occurs largely as a conse-

quence of active reabsorption of sodium or chloride. An alternative view of renal function pictures urine as the remainder of a filtration reabsorption operation not unlike that in other capillary beds of the body, modified by transport and permeability characteristics of the tubular wall. If this latter view is true, then a large percentage of tubular reabsorption must occur in an area of the tubule freely permeable to sodium and chloride as well as to water—and their concentration in tubular reabsorbate would closely reflect plasma concentration.

By infusing dogs with 150 cc. of 5 or 10 per cent sodium chloride followed by administration of normal saline solution at 5 cc./minute, steady high levels of sodium (circa 200 mEq./L.) and chloride (circa 130 mEq./L.) were attained. Comparison of tubular reabsorption at near normal values with reabsorption of sodium and chloride at high plasma concentrations revealed that the tubules reabsorbed more sodium and chloride in the latter instance. These data are interpreted as favoring the view that a large fraction of glomerular filtrate is reabsorbed in an area of the tubule freely permeable to sodium and chloride as well as to water.

STUDIES OF STRUCTURE-FUNCTION RELATIONSHIPS OF STEROIDS: THE 16-METHYLCORTICOSTEROIDS. *Herbert A. Burke, Jr. and Grant W. Liddle.** Dept. of Medicine, Vanderbilt Univ. School of Medicine, Nashville, Tenn.

Previous studies have demonstrated that relatively minor changes in the chemical structure of corticosteroids may result in major alterations in biologic activity. For example, the introduction of halogen atoms in the 9-alpha-position of the corticosteroid nucleus results in a general increase in potency of the compound. The introduction of a double bond between carbon atoms 1 and 2 results in enhancement of all corticosteroid functions except those concerned with electrolyte metabolism. Introduction of a methyl group in 2-alpha-position results in enhancement of the electrolyte-regulating activity of 11-beta-hydroxy-corticosteroids. The remarkable anti-inflammatory potency of 16-alpha-methyl-9-alpha-fluoro-prednisolone has stimulated interest in the biologic consequences of introduction of the 16-methyl group into the corticosteroid molecule.

The metabolic, hematologic and endocrinologic effects in man of 16-methyl-corticosteroids have been compared with their respective non-methylated analogs. The following general conclusions have been drawn:

(1) In all instances studied, 16-alpha-methylation attenuates the sodium-retaining and potassium-losing effect of corticosteroids.

(2) 16-Alpha-methylation enhances eosinopenic, nitrogen-wasting and ACTH-suppressing activity of corticosteroids.

(3) 16-Beta-methylation appears not to alter the activity of prednisone.

(4) The metabolic fate of 16-alpha-cortisol appears to differ from that of cortisol itself, since little of it appears in the urine as a 17,21-dihydroxy-20-ketosteroid glucuronide.

FURTHER STUDIES ON CARBOHYDRATE METABOLISM IN PANHYPOPITUITARISM. *Thomas W. Burns.* Dept. of Medicine, Univ. of Missouri School of Medicine, Columbia, Mo.

Serial insulin-glucose tolerance tests (IGTT) were performed in three patients with untreated panhypopituitarism. In two patients receiving daily infusions of ACTH the response following glucose was enhanced within forty-eight hours without change in the response to insulin. Comparable curves were obtained during cortisone administration in the third patient. After being on replacement therapy for ten months, one patient was rehospitalized. Maintenance cortisone therapy was withheld for a period of four days, then 100 mg. cortisol was administered intravenously and maintenance cortisone therapy resumed; five days later cortisol was administered again. Two IGTT curves obtained while the patient was not receiving cortisone and one obtained immediately after the first administration of cortisol were comparable to the control curve. A curve obtained after the second dose of cortisol revealed elevation in the fasting glucose level but no change in the magnitude of the response to insulin.

The findings suggest that in the fasting state the ability of insulin to lower blood sugar is not impaired by levels of adrenal steroids sufficient to increase the response to orally administered glucose. Patients chronically depleted of adenohypophyseal hormones demonstrate prompt reaction to slight increase in corticoids, while acute deprivation of corticoids failed to alter the IGTT in the maintained patient.

CHANGES IN PHOSPHORUS HOMEOSTASIS, FOLLOWING PARATHYROIDECTOMY IN MAN. *John J.*

*Canary and Laurence H. Kyle.** Dept. of Medicine, Georgetown Univ. School of Medicine, and Georgetown Univ. Hospital, Washington, D. C.

Following parathyroidectomy, serum calcium decreases to tetanic levels prior to increase of serum phosphorus, thus supporting the concept that parathyroid hormone has a direct skeletal effect and indicating an indirect or delayed action on phosphorus. This problem was evaluated by parallel measurements of serum and urinary calcium and phosphorus in four patients in whom hypoparathyroidism developed following thyroid surgery. In all cases tetanic manifestations preceded elevation of serum phosphorus. A profound fall in phosphorus excretion—demonstrated by a low phosphate clearance (Cp)—occurred soon after surgery. In two subjects with transient tetany, Cp decreased prior to elevation of serum phosphorus and returned to normal before regression of the hyperphosphatemia. In the instances of permanent parathyroid deficiency changes were even more marked; one patient with severe hypocalcemic tetany demonstrated no elevation of serum phosphorus until the third postoperative day; however, Cp was only 0.3 ml./minute on the day after surgery. These studies offer further evidence for a dual action of parathyroid hormone but indicate that changes in phosphorus excretion occur with equal or greater rapidity than those of serum calcium. The delayed elevation of serum phosphorus in hypoparathyroidism can be attributed to the magnitude of the phosphate compartment.

CLINICAL AND PHYSIOLOGICAL STUDIES IN SIX PATIENTS WITH MYOCARDIAL ANEURYSMS SUCCESSFULLY RESECTED, EMPLOYING THE CARDIOPULMONARY BYPASS. *Don W. Chapman** *and Denton A. Cooley.* Dept. of Medicine and Surgery, Baylor Univ. College of Medicine, Houston, Texas.

Myocardial aneurysms have been successfully resected in six patients, employing the cardiopulmonary bypass. All involved the left ventricle. Persistence of ST segment elevation on electrocardiographic tracings was noted in all six. Teleroentgenograms, laminograms and angiograms were used to delineate their location.

Five patients had cardiac catheterization preoperatively and were found to have elevated pulmonary and right ventricular pressures, and reduced cardiac output. In two, catheterization has been performed since the operation; right-sided pressures have returned to normal, and the cardiac output has improved.

The high incidence of congestive failure, rhythm disturbances, thromboembolic phenomena and shock in myocardial aneurysm should be reduced with this procedure. Four patients have returned to work; two others are still convalescent. There have been no deaths to date.

ATHEROSCLEROSIS IN PIGEONS—ITS SPONTANEOUS OCCURRENCE AND RESEMBLANCE TO ATHEROSCLEROSIS IN MAN. *T. B. Clarkson, R. G. Prichard, M. G. Netsky and H. B. Lofland.* The Vivarium and Dept. of Pathology, Neurology and Biochemistry, Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, N. C.

In certain breeds of pigeons (auto-sexing Kings, Silver Kings and White Carneaux) atherosclerosis develops spontaneously. The disorder is nearly identical with the disease in human beings. In another breed of pigeons (Show Racers), kept under the same conditions of diet, housing and exercise, there was almost no atherosclerosis.

The plaques are raised, yellow, intimal lesions projecting into the lumen. The lesions are macroscopically sudanophilic. Calcification and ulceration were not uncommonly associated with the lesion.

The microscopic features of the lesions were strikingly similar to those found in man. The plaques contain large amounts of free and intracellular sudanophilic material, cholesterol crystals and calcium salts which are separated from the lumen by a layer of proliferated connective tissue. There was disruption of the elastic tissue in the area of the plaques.

Serum total, free and ester cholesterol, and phospholipides were determined for all birds. There were no significant differences in serum lipide levels among the four breeds of pigeons despite marked differences in the severity of atherosclerosis. The aorta weight and its cholesterol content paralleled the severity of atherosclerosis.

The diet consumed by these pigeons was corn, wheat, peas and kafir (milo).

BILIARY EXCRETION OF BROMSULFALEIN (BSP) AS A CONJUGATE OF GLYCINE AND GLUTAMIC ACID. *Burton Combes.* Dept. of Internal Medicine, Univ. of Texas Southwestern Medical School, Dallas, Texas.

Although the BSP test is generally considered to be the most sensitive means of detecting liver disease, the mechanisms by which BSP is taken up and excreted by the liver are poorly understood. An analysis of BSP-excretory products appearing in rat bile after intravenous administration of this dye was therefore undertaken. Filter paper chromatographs of such bile showed four distinct BSP bands. The major band, designated "BSP-A," accounted for approximately three-quarters of the excreted dye. It is definitely not a glucuronic acid conjugate. Hydrolysis of BSP-A yielded, on rechromatographing, BSP and two ninhydrin spots. The latter were identified as glycine and glutamic acid by paper chromatography of the free amino acids; this was confirmed by identifying their dinitrophenyl derivatives.

These data indicate that BSP is excreted into bile predominantly as a conjugate of the amino acids, glycine and glutamic acid, and suggest, therefore, that the BSP test is a measure of amide formation in the liver.

INHIBITION OF ALDOSTERONE SECRETION AND MODIFICATION OF ELECTROLYTE EXCRETION BY A CHEMICAL INHIBITOR OF 11β-HYDROXYLATION. *William S. Coopage, Jr., Donald Island and Grant W. Liddle.** Dept. of Medicine, Vanderbilt Univ. School of Medicine, Nashville, Tenn.

Previous investigations have shown that 2-methyl-1,2-bis-(3-pyridyl)-1-propanone (SU-4885) inhibits 11β-hydroxylation by the adrenal cortex, thus impairing secretion of cortisol and corticosterone, and leading to secretion of 11-desoxycortisol (compound S) and 11-desoxycorticosterone (DOC). Prednisone, administered in doses sufficient to suppress ACTH, will suppress secretion of compound S and DOC. The steroid pattern resulting from treatment with SU-4885 is similar to that in hypertensive congenital adrenal hyperplasia; it seemed of interest, therefore, to study in detail the effects of SU-4885 upon mineralocorticoid secretion and electrolyte metabolism. Results: (1) In persons on liberal sodium intake, SU-4885 induced increased secretion of DOC and renal retention of sodium. (2) In persons on liberal sodium intake and doses of prednisone sufficient to suppress ACTH, SU-4885 induced no significant secretion of DOC and no renal retention of sodium. (3) In persons with hyperaldosteronism (receiving prednisone to preclude DOC secretion), SU-4885 induced striking decreases in urinary levels of aldosterone and the aldosterone metabolite, pregnane-3,18,21-triol-11,20-dione. This was accompanied by natriuresis. Conclusions: SU-4885 inhibits adrenocortical synthesis of one sodium-retaining steroid, aldosterone, but (unless ACTH is suppressed) induces secretion of another sodium-retaining steroid, DOC. The effects of SU-4885 upon electrolyte metabolism represent the resultants of interaction of these two factors.

DIFFERENTIATION OF RIGHT VENTRICULAR FLOW LOADS FROM PRESSURE LOADS. *E. E. Eddleman, Jr.** *and H. Duke Thomas.* Dept. of Medicine, Medical College of Alabama, and Medical Service, V. A. Hospital, Birmingham, Ala.

Thirty-five patients studied include twenty patients with mitral stenosis, eleven with interatrial septal defect, two with pulmonic stenosis, and two with isolated pulmonary hypertension. Electrocardiograms were normal in 29 per cent of the patients, and fluoroscopic examinations were within normal limits in 26 per cent. Kinetocardiograms demonstrated a prominent early and mid-systolic outward movement of the precordium in all patients with mitral stenosis and elevated pulmonary artery pressures; however, in this group 50 per cent had normal electrocardiograms and 40 per cent had no enlargement of the right ventricle on fluoroscopic examination. Patients with interatrial septal defects and significant pulmonary hypertension had a prominent mid-systolic outward movement in the kinetocardiogram which was absent in those with normal pulmonary artery pressures. Kinetocardiographic traces with and without pulmonary artery pressure elevations can be differentiated by the ratio of the amplitude of the initial outward movement to the systolic retraction, the ratio being one or greater in patients with pulmonary hypertension and less than one in patients without pulmonary hypertension. Also the duration of the outward movement was never greater than .26 second in patients without pulmonary hypertension whereas the duration ranged from .30 to .46 second in patients with pulmonary hypertension. Thus it is possible to differentiate right ventricular pressure loads from flow loads by the kinetocardiographic technic whereas the electrocardiograms and fluoroscopic examinations were less reliable.

EFFECT OF OPERATIVE POSITION ON VENTILATION DURING ETHER ANESTHESIA. *Leonard W. Fabian,*

William A. Neely and Jasper L. McPhail. Dept. of Surgery and Anesthesia, Univ. of Mississippi School of Medicine, Jackson, Miss.

The purpose of the study was to evaluate the effects of operative position upon ventilatory efficiency utilizing various anesthetic compounds and allowing spontaneous unassisted respiration.

In the initial phase of the study, ether anesthesia was employed in four adult patients who were all considered good anesthetic and surgical risks. The surgical procedures were those involving areas which would not ordinarily interfere with respiratory efficiency. Minute volumes were measured continuously before and during anesthesia by an integrating pneumotachometer. Arterial blood gas studies including pH, pCO_2, and O_2 were obtained.

Data were obtained before intravenous premedication, fifteen minutes after premedication, fifteen minutes after intubation, fifteen minutes after placing the patient in a 15° Trendelenberg position, and ten minutes after returning the patient to the control position.

It was found that a 15° Trendelenberg position produced no significant ventilatory change.

CHANGES IN HEART RATE DURING INFUSION WITH LEVARTERENOL: AN INDEX OF ARTERIAL ELASTICITY. *Frank A. Finnerty,* George Hajjar, Martin L. Ryan, Gloria Massaro* and John Tuckman.* Dept. of Medicine, Georgetown Univ. School of Medicine, and Georgetown Univ. Medical Div., D. C. General Hospital, Washington, D. C.

Studies in this laboratory have demonstrated varying responses in heart rate during infusion with levarterenol independent of the age of the patient, the control level or percentage increase in the arterial pressure. Greater than a 20 per cent increase in mean arterial pressure in fifty-five patients without cardiovascular disease, sixteen hypertensive patients without sclerosis and fifteen patients with pregnancy toxemia was accompanied by more than a 15 beat per minute reduction in heart rate in each patient. No change in heart rate followed a comparable increase in arterial pressure in twelve patients with hypertensive cardiovascular disease and in fourteen normotensive arteriosclerotic patients.

Failure of response to levarterenol with bradycardia could result from a defect in the efferent or afferent limb of the reflex or in the walls of the aortic arch. The production of tachycardia by the administration of atropine in all patients indicates the intactness of the efferent limb. The greater increase in pulse pressure during infusion with levarterenol, and the decrease in pulse pressure during infusion with amyl nitrite in the patients in whom bradycardia due to levarterenol did not develop argue for a defect in the walls of the baroreceptor-containing vessels, e.g., a sclerotic process preventing expansion during systole. Changes in the heart rate during infusion with levarterenol, therefore, might serve as an index of aortic elasticity.

A STUDY OF THE IMMUNOLOGIC PROPERTIES AND CYTOTOXIC ACTIVITY OF ANTITUMORAL AUTOANTIBODIES IN PATIENTS WITH MALIGNANT TUMORS. *James W. Finney, Russell H. Wilson,* Dale A. Clark and Ernest E. Byers.* Univ. of Texas Southwestern Medical School and V. A. Hospital, Dallas, Texas.

Evidence for the existence of antitumoral autoimmunity in patients with cancer has stimulated scientists of many disciplines to do research in this field. In experimental animals immunity to malignant tumors has been demonstrated. In man, Graham has demonstrated serum antibody-like proteins which react with the patient's own tumor protein fraction. Radiotherapy and injections of homogenized tumor increased the magnitude of the host's autoimmune response.

The thought of inducing immunity to a patient's own cancer protein fraction has led us to investigate this discipline in conjunction with conventional therapy.

The tannic acid hemoagglutination test was used to measure blood antibody levels in five terminal patients with malignant tumors who had measurable subcutaneous nodules before, during and after immunization against his own tumor protein fractions.

If the magnitude of local tissue antibody titer could be increased sufficiently, one could demonstrate the degree of cytotoxicity of antitumoral autoantibodies.

Cohn fractions I, II and III were concentrated and injected into experimental lesions. Saline and suspensions of normal Cohn fractions I, II and III were injected in and around measurable control subcutaneous nodules. Biopsy specimens showed that cancer cells exposed to high concentrations of antitumoral antibodies underwent atrophy and necrosis whereas control nodules did not reveal significant cellular changes.

CLINICAL PHARMACOLOGY OF FLUMETHIAZIDE, AN ORALLY EFFECTIVE DIURETIC AND ANTIHYPERTENSIVE AGENT. *Ralph V. Ford,* A. C. Montero and J. B. Rochelle, III.* Dept. of Medicine and Pharmacology, Baylor Univ. College of Medicine, and Medical Service of V. A. Hospital, Houston, Texas.

Flumethiazide [6-(trifluoromethyl)-1,4,2-benzothiadiazine-7-sulfonamide,1,1-dioxide] differs structurally from chlorothiazide in the presence of the tri-fluro group in place of the chloride. We have used previously described technics for the bioassay of diuretic potency, electrolyte excretion effects, serum biochemical changes, repetitive effectiveness and antihypertensive potency. The antihypertensive effects were observed in twenty-five outpatients while all other studies were carried out under controlled metabolic conditions.

Flumethiazide administered in doses of 1.0 and 2.0 gm., orally, is 0.7 times as potent as meralluride (Mercuhydrin®), intramuscularly, as a natriuretic agent. (Diuril is 0.8 times as potent.) However, there is an increase in sodium excretion at doses as low as 250 mg. The effects on electrolyte excretion are similar to those observed after the administration of chlorothiazide (primarily changes in sodium and chloride, with small changes in potassium and bicarbonate). The drug is repetitively effective on continuous daily use and produces minor disturbances in serum biochemical architecture similar to that of chlorothiazide. There is no significant difference in its antihypertensive potency from that of chlorothiazide.

Flumethiazide appears to be another valuable agent in the management of edema and hypertension.

INVESTIGATIONS CONCERNING THE STAPHYLOCOCCAL PROBLEM IN HOSPITALS. *James B. Grogan and Curtis P. Artz.** Surgical Bacteriology Laboratory and Dept. of Surgery, Univ. of Mississippi School of Medicine, Jackson, Miss.

Phage type and sensitivity patterns were determined on staphylococci from two groups: (1) nose and throat cultures isolated from patients and (2) clinical infections. Sixty-five per cent of hospital patients harbored coagulase-positive staphylococci of which 65 per cent were resistant to treatment with one or more antibiotics. Resistant 80–81 strains were found to be carried by 20 per cent of the patients.

In 477 coagulase-positive cultures of staphylococci isolated from patients with various infections, 73 per cent were resistant to treatment with one or more antibiotics. Strain 80–81 was found in 22 per cent of these patients. A comparison of the resistant patterns between the two groups indicates that 80–81 strains from patients with infections are more resistant than those from cultures of the nose and throat.

When varying dilutions of staphylococci were injected intraperitoneally into mice the 80–81 strains appeared to kill more in high dilution.

Control of infections requires constant attention to phage type and resistant patterns. The disc method has proved to be satisfactory for screening and an improved method permits the phage typing of 100 cultures daily.

STAPHYLOCOCCAL BACTEREMIA IN DOGS: EFFECT OF UREMIA, SPLENECTOMY, AND SPLENECTOMY PLUS PORTACAVAL SHUNT ON THE RATES OF CLEARANCE FROM THE BLOOD STREAM. *James B. Grogan, Richard S. Doyle and James D. Hardy,** Dept. of Surgery, Univ. of Mississippi Medical Center, Jackson, Miss.

Normal dogs, dogs with uremia, splenectomy, and splenectomy plus portacaval shunt were injected intravenously with 5 cc. of a heavy saline suspension of a coagulase-positive strain of Staphylococci aureus. Serial blood samples were taken from the femoral vein, diluted in sterile saline and plated.

The results from at least three dogs in each group have been studied and the clearance curves plotted on semilogarithmic paper. There was little difference in the first phase of clearance in the different groups. After a rapid initial clearance rate within the first thirty minutes, clearing was continued at a much slower rate. Bacteremia appeared to persist at a higher level in animals having splenectomy and portacaval shunt than in the normal control animals. While in the normal dogs the blood stream was sterile before injection, after injection bacteremia persisted for days until it finally cleared or until the defense mechanisms of the hosts were overcome and death occurred.

PULMONARY RESECTION: EFFECT OF INITIAL VEIN LIGATION UPON SEQUESTRATION OF BLOOD IN LUNG. *James D. Hardy,* James T. Croley and James P. Spell.* Dept. of Surgery, Univ. of Mississippi Medical Center, Jackson, Miss.

There are two reasons why it would be desirable to divide a pulmonary vein prior to ligation of the artery in performing pulmonary resection. First, in lobectomy of the upper right lung, the arterial supply is often partially obscured by branches of the superior vein. In certain patients lobectomy would be facilitated by initial division of these veins. Second, in the presence of malignancy, tumor cell embolization would be diminished by initial vein ligation, prior to manipulation of the lung. Unable to find data in the literature regarding the volume of blood trapped in the lung by initial vein ligation, we have conducted the following studies.

Lobectomy of the upper right lung was performed in thirty adult dogs of comparable size. Ten had initial venous ligation, ten initial arterial ligation, and ten simultaneous arterial and venous ligation. Following thirty minutes of venous or arterial occlusion in groups I and II, the entire base of the lung was abruptly divided between clamps and the weights of the right lung in the three groups were compared. The average weights of the right lungs were: group I, 139.2 gm.; group II, 108.1 gm.; and group III, 123.5 gm. The difference between group I and group II is statistically significant. It is concluded that initial ligation of the venous supply to the upper right lung in a 75 kg. man might result in the sequestration of perhaps 150 cc. of blood. This volume of blood loss may be justifiable as a prophylaxis against cancer cell dissemination.

PARADOXICAL (FORWARD) MOVEMENTS OF THE PRECORDIUM DURING EJECTION. *Tinsley R. Harrison.** Dept. of Medicine, Medical College of Alabama, Birmingham, Ala.

Five forward motions during ejection have been found in a study of normal subjects (twenty) and patients with mitral stenosis (sixteen), cor pulmonale (four), mitral insufficiency (ten), or other disorders causing left ventricular hypertrophy (sixteen). (1) The previously described motion of recoil as ejection starts. (2) Inconstant outward movements in the upper interspaces, beginning about .03 second later and ascribed to impact on the great vessels. (3) Outward motion in the right (and sometimes the left) parasternal area, starting about .07 second after ejection. This is attributed to rightward and forward rotation by the right ventricle, because it is exaggerated in subjects with right ventricular hypertrophy. (4) Small forward motion over the entire precordium, starting about .12 second after ejection. Because it is exaggerated in patients with mitral insufficiency, this movement is ascribed to atrial filling which may predominate over ventricular emptying at this time. (5) Complex and variable motions occurring about .17 second after ejection begins. These are usually increased in patients with left ventricular hypertrophy, and are attributed to shape and positional changes induced by terminal contraction of the left ventricle.

Palpation of these movements may be of value in the clinical recognition of ventricular hypertrophy. Normal motions and those due to hypertrophy must be distinguished from those due to ischemic bulges in patients with coronary disease.

THE EFFECT OF HYDROCORTISONE ON MULTIPLICATION OF THE TUBERCLE BACILLUS IN VITRO. *Allen R. Hennes, Hubert McClure, Harold G. Muchmore and James F. Hammarsten.** Dept. of Medicine, V. A. Hospital, and Univ. of Oklahoma School of Medicine, Oklahoma City, Okla.

That large doses of hydrocortisone may decrease resistance to infection with M. tuberculosis in man and in various animals is well established. However, the effect of hydrocortisone on M. tuberculosis in vitro is largely unknown and unexplored.

We have studied the effect of 3 concentrations of free hydrocortisone on turbidimetric growth of the tubercle bacillus in a synthetic culture medium. In each of 6 strains, 100 mcg./ml. of hydrocortisone produced approximately 80% slowing of growth rate as compared to the control. None of the strains grown in this concentration of hydrocortisone has shown a logarithmic growth phase. 10 mcg./ml. has in some strains produced a prolongation in generation time. 1 mcg./ml. is without apparent effect on growth rate. INH sensitive and resistant strains were affected equally. Whether concentrations of hydrocortisone lower than 100 mcg./ml. can produce this apparent bacteriostatic effect is at present unknown.

It is possible that the total effect of adrenal steroids on clinical tuberculosis may be a resultant of suppressant effects on multiplication of the bacillus and suppression of the defensive mechanisms of the host, the latter predominating under usual circumstances.

Bacterial systems of this type may serve as useful experimental models for studying steroid effects.

SIGNIFICANCE OF METAMORPHOSED ERYTHROCYTES IN SICKLE CELL ANAEMIA. *G. Hilkovitz.* Dept. of Medicine, Medical College of Virginia, Richmond, Va.

Several authorities concur that the numbers of "sickled cells" in venous blood bear no relationship to the clinical and hematological state. Some apply the term "sickled cell" to all misshapen erythrocytes; others reserve this description for crescentic cells pointed at each end.

Venous blood was removed anaerobically and fixed in formol saline. Smears were stained with eosin, and 500 cells were counted in each of 224 smears obtained from twenty-three patients. Erythrocytes were classified as follows: (1) classically sickled (2) other metamorphosed cells and (3) normal.

In patients severely affected 15 per cent or more of cells were classically sickled and less than 30 per cent of cells were normal. In the same patient the numbers of classically sickled cells did not vary proportionately with the severity of the disease. The other metamorphosed cells increased in number and normal cells decreased in number in the same patient during periods of increased severity of the disease. It was concluded that the numbers of normal cells and of cells not classically sickled varied proportionately with the clinical and haematological state.

STUDIES ON THE ESTROGEN-SENSITIVE ENZYME SYSTEM FROM PLACENTA. *Nina Hollander, Vincent P. Hollander and Joseph D. Brown.* Dept. of Internal Medicine and Dept. of Biochemistry, Univ. of Virginia School of Medicine, Charlottesville, Va.

The enzyme system in placental homogenates which is stimulated *in vitro* by estradiol-17B has been described by several investigators. This report consists of studies on the role of TPN in this system and a comparison between properties of the estradiol-sensitive placental enzyme system and the 17β-hydroxy-steroid dehydrogenase.

Preparation of the enzyme system and the assay for the estradiol effect on the α-ketoglutarate production from isocitrate have been described. In order to measure the rate of the 17β-hydroxy-steroid dehydrogenase at a steroid concentration of 3×10^{-6} M, it was necessary to employ fluorimetric or radioactive technics. Dialyzed enzyme refers to 20 per cent placental homogenate in 0.25 M sucrose dialyzed against 40 volumes of 0.25 M sucrose with 0.001 M phosphate buffer at pH 7.0. Purified enzyme was precipitated by adding an equal volume of saturated ammonium sulfate solution to the dialyzed enzyme.

The transhydrogenase and the 17β-hydroxy-dehydrogenase systems had the following points of similarity: (1) A similar pH curve in both phosphate and Tris buffers, and a shift in pH maximum from 6.8 to 7.8 in phosphate on addition of TPN. (2) Instability toward acid not due to destruction of TPNH. (3) Inhibition by TPN concentrations above 0.005 mM. (4) Inhibition by 2′ adenylic acid, not reversed by TPN.

Because of the complexity of requirements, the assay for the estrogen-sensitive enzyme is aided by the greater sensitivity of the direct fluorimetric method and the availability of 2′ adenylic acid as inhibitor.

IN VITRO LIPID SYNTHESIS AND NON-ESTERIFIED FATTY ACID CONTENT OF ADIPOSE TISSUE FROM MICE IN A VARIETY OF NUTRITIONAL STATES. *Guy Hollifield* and William Parson.** Dept. of Internal Medicine, Univ. of Virginia School of Medicine, Charlottesville, Va.

Rats trained to eat all of their daily ration in three hours show an alteration in respiratory quotient which has been interpreted as evidence of enhanced ability to convert carbohydrate to fatty acid in extrahepatic as well as hepatic tissue (Brobeck et al.). Using deuterium, Shapiro and Wertheimer demonstrated that rat adipose tissue incorporated more deuterium *in vitro* when the rat had been subjected to dietary manipulation designed to enhance lipid synthesis.

We have studied the *in vitro* lipid synthesis of adipose tissue from C^{14} acetate and non-esterified fatty acid content of adipose tissue of mice fed *ad libitum*, fasted sixteen hours, fasted sixteen hours and fed for two hours, and fed only two hours per day for five to seven days. The technic described by Baruch and Chaikoff was used for the study of *in vitro* lipid synthesis and non-esterified fatty acids were determined by a modification of Dole's method.

Mice limited to a two-hour feeding each day for five to seven days had a striking increase in lipid synthesis and a fall in the non-esterified fatty acid of adipose tissue compared with fasted mice who had a high non-esterified fatty acid content of adipose tissue and low lipid synthesis. Mice fed for two hours after a sixteen hour fast

(previously fed *ad libitum*) had low non-esterified fatty acid levels and low lipid synthesis.

These studies show that the non-esterified fatty acid content of adipose tissue is generally low when lipid synthesis is high and that training by limiting feeding time may markedly enhance lipid synthesis. These findings are consistent with the idea that enzyme systems in adipose tissue cells involved in lipid synthesis show adaptive changes.

USE OF EXCHANGED CITRATED BANK BLOOD TO PRIME AN EXTRACORPOREAL CIRCUIT. *Phyllis R. Ingram, James B. Littlefield, and William H. Muller, Jr.** Dept. of Surgery, University of Virginia School of Medicine, Charlottesville, Va.

A problem encountered with the use of an extracorporeal circuit is that of obtaining fresh blood shortly before initiation of the procedure. Infusion of citrated bank blood into the subject for operation immediately prior to surgery allows withdrawal of equivalent amounts of patient blood into heparinized bottles for use in priming the extracorporeal circuit. The danger of rapid administration of large amounts of cross-matched mixed donor blood under anesthesia is recognized.

This hypothesis was tested in fourteen anesthetized dogs by exchanging citrated bank blood from one or more donors, with eleven survivors. Transfusion reactions occurred in two animals, but the exchange was deliberately continued and resulted in death. One death occurred from technical error. Exchanges over a period of thirty to ninety minutes varying from 500 cc. to 1,000 cc. in many cases approximated total blood volume. Blood balance was maintained within a range of 100 cc. Routine blood and platelet counts, prothrombin times, hemolysis and fibrinogen studies performed before and after exchange, and during and after bypass were all within safe limits. Citrate levels and pH studies were performed in some procedures. Continuous systemic arterial pressures and electrocardiographic changes were recorded. The period during infusion of citrated blood in several animals not covered by calcium was accompanied by convulsions, hypotension and electrocardiographic changes which responded to the administration of calcium gluconate indicating the necessity for calcium gluconate coverage. The pH of the donor blood, which was low, approached the normal range in exchanged blood. High levels of citrate were present in exchanged blood.

This technic appears to be an effective method of providing blood to prime an extracorporeal circuit.

DIFFERENCES IN NATURALLY OCCURRING ARTERIAL ANASTOMOSES OF NORMAL AND PATHOLOGICAL HUMAN HEARTS. *Thomas N. James and George E. Burch.** Dept. of Medicine, Tulane Univ. School of Medicine, New Orleans, La.

One of the major problems in evaluating procedures designed to increase the blood supply to the heart is how to decide if created anastomoses function or not. Recent claims have been made that numerous small anastomoses are created by pericardial poudrage, by internal mammary artery implantation into the myocardium, as well as by other procedures. But the mere demonstration of these anastomoses imparts no information as to whether or not they actually increase the collateral circulation.

In a group of eighty-two human hearts studied by vinylite injection and hydrochloric acid corrosion certain characteristics of the arterial anastomoses were observed. Two general types were found, ones which were straight or nearly so, and others which were extremely tortuous and elongated. The former type were present both in normal hearts and in hearts with coronary occlusion and myocardial infarction, although they tended to be of larger caliber in the infarcted hearts. The latter type, extremely tortuous arteries whose characteristics were consistent with functioning vessels, were found only in infarcted hearts and were often more than 1,000 μ. in diameter; when present they were numerous and formed connection with neighboring patent arteries in all directions. Histologic slides were prepared from myocardium distal to the occlusion in the infarcted hearts.

It is likely that the anatomic characteristics of naturally occurring and artificially created anastomoses may indicate the nature of their function, a factor surely of more significance than the number of vessels alone.

THE EFFECT OF β-SITOSTEROL, LINOLEIC AND LINOLENIC ACID, AND ESTRADIOL VALERATE UPON EXPERIMENTALLY INDUCED HYPERCHOLESTEROLEMIA AND THE DEVELOPMENT OF ATHEROMATOUS CHANGE IN THE DOG. *George L. Jordan, Jr.,** *Don M. Chapman,** *Michael E. DeBakey** *and Bela*

Halpert. The Cora and Webb Mading Dept. of Surgery and Dept. of Medicine and Pathology, Baylor Univ. College of Medicine, and V. A. Hospital, Houston, Texas.

A homograft was placed in the abdominal aorta of each of sixteen dogs. Hypothyroidism was induced with radioactive iodine, and all animals were fed a diet containing 5 per cent cholesterol. The dogs were divided into four equal groups. One group served as controls. β-sitosterol was administered orally to the animals in the second group and linoleic and linolenic acid to those in the third. The fourth group was treated with estradiol valerate administered intramuscularly once weekly.

All animals in the first, third and fourth groups maintained high average serum cholesterol concentrations, ranging from 504 mg. per cent to 1,421 mg. per cent, for periods of twelve to forty-six weeks; in some animals in each group atheromatous changes developed. The average serum cholesterol concentrations of the dogs in the second group ranged from 231 mg. per cent to 439 mg. per cent; atheromatous changes did not develop in any of these animals. Thus under the conditions of this experiment neither unsaturated fatty acids nor estradiol valerate prevented the development of hypercholesterolemia or atheromatous change. The results with β-sitosterol are inconclusive for the animals ate poorly, so that low serum cholesterol concentrations may only represent an inadequate intake of cholestrol.

STUDIES ON THE ROLE OF PERIPHERAL SUPERFICIAL LYMPHATICS OF MAN AND THE DOMESTIC RABBIT IN THE TRANSPORT OF LIPIDS. *R. A. Jordan and S. A. Threefoot.** Dept. of Medicine, Tulane Univ. School of Medicine, and the Research Laboratory, Touro Infirmary, New Orleans, La.

To study uptake of lipids by cutaneous lymphatics, various oils tagged with Oil Red O or Sudan Black were injected into transilluminated rabbits' ears. Unless forced into lymphatics by injection or massage, there was no visible movement or active transport of oil. None was observed in blood vessels.

While intradermal aqueous Patent Blue V was absorbed and produced lymphatic streamers in human subjects, Sudan Black labeled sesame oil did not. Disappearance of oil from injected sites in several weeks indicated very slow removal, probably via lymphatics, as in rabbits' ears.

Intradermal radioiodinated triolein gave disappearance half-times of three to four weeks as contrasted to those of one to two days for radioiodinated albumin. No significant counts appeared in blood and only approximately 10 per cent of administered radioactivity was recovered in urine in six days.

It is concluded that during the periods of study, cutaneous lymphatics did not participate actively in transport of unaltered lipid. Since movement of lipids from injection sites was slow, it seems likely that chemical alteration and/or mechanical stimulation must occur before lipid traverses vascular membranes for removal. It is recognized that lipids of other physicochemical characteristics (molecular size, viscosity, mobility) may perform differently.

HIGH FREQUENCY ATRIAL POTENTIALS. *George A. Kelser, Jr. and Cesar A. Caceres.* Dept. of Medicine, George Washington Univ. Medical School, Washington, D. C.

Abrupt cyclical bursts of rapid electrical activity can be recorded from intracavitary electrodes from the right and left atria of man with amplifiers capable of standardization sensitivities up to 500 mm./mv. Rapid potential changes recorded from right atrium occur approximately 0.04 second after the onset of limb lead P wave and with the onset of rise of right intra-atrial pressure. Rapid potential changes recorded from left atrium occur after the peak of limb lead P wave with the onset of rise of left intra-atrial pressure.

Results of wave frequency and harmonic content analysis of the rapid potential changes by electronic filters indicate the presence of frequencies exceeding 400 cps. Conventional electrocardiographic amplifiers cannot faithfully register electrical activity above 50 cps.

While the configuration of the conventional intracavitary P wave and its intrinsic deflection varied considerably with changes in electrode position, the bursts of rapid electrical activity remained more constant in relation to limb lead P waves and atrial pressure pulse contours. When the intrinsic deflection of the conventional intracavitary P wave coincided with the high frequency spikes, the intrinsic deflection was inscribed rapidly. When the intrinsic deflection and the high frequency spikes did not coincide, the intrinsic deflection was inscribed more slowly.

Although the significance of these previously

unrecognized bursts of rapid electrical activity remains to be determined, consideration must be given to their contribution to the final form of the conventional electrocardiographic P wave, and particularly to the intrinsic deflection in intracavitary leads.

ALTERATIONS IN PULMONARY FUNCTION IN MYOTONIC AND PROGRESSIVE MUSCULAR DYSTROPHY. *K. H. Kilburn, J. T. Eagen, H. O. Sieker* and A. Heyman.** Dept. of Medicine, Duke Univ. School of Medicine, and V. A. Hospital, Durham, N. C.

Although cardiac involvement is frequently noted in patients with muscular dystrophy, little attention has been given to the pulmonary complications in this disorder. Ventilatory functions, blood gas determinations and effects of carbon dioxide inhalation were studied in nine patients with myotonic dystrophy and in eight with progressive or facioscapulohumeral muscular dystrophy. These two types of dystrophies differ in the mechanism of their pulmonary dysfunction. All but one patient with myotonic dystrophy had an elevation of carbon dioxide tension greater than 45 mm. Hg with a mean of 49 mm. Hg and a minute ventilation of 6.3 L. In muscular dystrophy the mean pCO_2 was 43 mm. Hg with a minute ventilation of 7.3 L. The mean vital capacity was 90 per cent and maximum breathing capacity 75 per cent in myotonic dystrophy, compared with 71 per cent and 58 per cent, respectively, in patients with muscular dystrophy. In myotonic dystrophy, the response to carbon dioxide inhalation was slightly less than in progressive muscular dystrophy.

This study indicates that patients with myotonic dystrophy have hypoventilation and a decrease in respiratory center sensitivity possibly due to myotonia of the diaphragm and intercostal muscles which, however, permit adequate ventilation on effort. Patients with progressive muscular dystrophy with marked muscle weakness are able to maintain normal blood gases despite diminished pulmonary ventilation.

ANOMALOUS CHROMATOGRAPHIC BEHAVIOR OF HIGH MOLECULAR WEIGHT GAMMA GLOBULINS. *Joseph Lospalluto and Morris Ziff.* Dept. of Biochemistry and Medicine, Univ. of Texas Southwestern Medical School, Dallas, Texas.

Ion exchange chromatography of hyperglobulinemic serums on diethylaminoethyl (DEAE) cellulose has resulted in the separation of gamma globulin into components which differ in molecular size. In general, gamma globulin with a sedimentation coefficient of 7S (molecular weight, 150,000), which constitutes the major gamma globulin fraction in normal serum, appears as the first component in column effluents. Gamma globulins with sedimentation coefficients greater than 7S have appeared in subsequent effluents of the chromatogram. The 19S gamma globulin (molecular weight, 900,000) of normal and various abnormal serums has been eluted at the end of the chromatogram.

This technic has been applied to serums obtained from patients as follows: one normal patient, two with macroglobulinemia of the Waldenström type, one with multiple myeloma, and one with rheumatoid arthritis. In addition, the precipitate obtained by addition of heated Fraction II to rheumatoid serum was fractionated. The results obtained indicate that the chromatographic pattern of serum in conjunction with paper electrophoresis of the separated fractions offers a means of demonstrating the presence or absence of increased amounts of macroglobulins in lieu of ultracentrifugation. It has been possible in this way to differentiate between multiple myeloma and macroglobulinemia. The chromatographic technic has also made possible the preparation of pure 7S and 19S gamma globulins.

DETERMINATION OF SERUM QUINIDINE LEVELS AFTER ADMINISTRATION OF "LONG-ACTING" QUINIDINE. *John M. Lewis, Malcolm B. Daniell, A. Clark Griffin and Don W. Chapman.** Dept. of Medicine and Biochemistry, Baylor Univ. College of Medicine, Houston, Texas.

There is frequent need for adequately sustained levels of quinidine. In an attempt to work out a satisfactory method of maintaining this level, quinidine sulfate was compared with quinidine gluconate (specially treated) on various dosage schedules in some thirty patients. Also Benemid® was used to determine its possible influence on sustaining levels. Quinidine blood levels were determined by the method of Brodie and Udenfriend.

Quinidine sulfate was noted to produce higher but less sustained peaks reaching maximum heights at one to two hours and tapering off to control levels at four hours. Quinidine gluconate

peaked at two and a half to four and a half hours and fell off slowly after six hours, with the tapering less marked nocturnally. On the following morning, twelve hours after the last dosage, the quinidine levels tended to be approximately the same. Benemid was found markedly to augment the levels of both quinidine gluconate and sulfate. Hyperthyroidism in one patient was found to cause rapid increase of the turnover of quinidine, with maintenance of lower levels. Congestive heart failure and renal or hepatic dysfunction were noted to increase the serum levels of quinidine.

CLINICAL APPLICATION OF A NEW TEST OF "PITUITARY RESERVE." *Grant W. Liddle,* John W. Kendall, Jr., W. Carter Williams, Jr. and Alexander S. Townes.* Dept. of Medicine, Vanderbilt Univ. School of Medicine, Nashville, Tenn.

2-methyl-1,2-bis-(3-pyridyl)-1-propanone (SU-4885) inhibits 11β-hydroxylation by the adrenal cortex, resulting in decreased cortisol secretion. A "compensatory" increase in ACTH secretion then stimulates secretion of large amounts of biologically ineffectual 11-desoxycortisol (compound S) which gives rise to increased urinary 17-hydroxycorticoid values. This SU-4885-induced rise in 17-hydroxycorticoids has provided an index of the reserve capacity of the pituitary to secrete ACTH.

Five patients with frank panhypopituitarism failed to respond to SU-4885. Of five patients with chromophobe adenomas but without frank hypopituitarism, four failed to respond normally. Of four patients with acromegaly, two failed to respond. One patient with post-traumatic diabetes insipidus failed to respond. Three patients previously "cured" of Cushing's disease by pituitary radiation failed to respond. All patients cited except those with frank panhypopituitarism were responsive to exogenous ACTH; failure to respond to SU-4885 was therefore attributed to impaired responsiveness of the ACTH-secreting mechanism. Three patients with primary myxedema responded normally to SU-4885. Seven patients with untreated Cushing's disease due to adrenal hyperplasia exhibited excessive responses. Qualitatively different were three patients with Cushing's syndrome due to adrenal tumor, in whom SU-4885 induced decreases in urinary 17-hydroxycorticoids.

PLASMA FLOW IN THE RENAL PAPILLA. *Lawrence S. Lilienfield.** Dept. of Physiology, and Cardiovascular Research Laboratory, Dept. of Medicine, Georgetown Univ. Medical Center, Washington, D. C.

Reported investigations have recently demonstrated a large pool of exchangeable albumin in the renal papilla. In an attempt to determine whether much of this albumin is located intravascularly or in interstitial spaces, studies were performed on eleven anesthetized dogs. A constant infusion of I^{131} albumin was made into the ascending aorta. At specific intervals a loose ligature previously placed around the renal pedicle was suddenly tightened. The kidney was then removed and frozen rapidly. Weighed sections of papilla were assayed for radioactivity and compared with the average activity of arterial blood collected during the procedure.

From the data, the apparent volume of albumin distribution per 100 gm. of papilla could be calculated. One kidney was ligated at five seconds from the start of the infusion, and seven kidneys at ten seconds. An additional six kidneys were ligated at fifteen seconds, and seven kidneys at sixty seconds. When the volumes were plotted against time, a simple linear relationship was noted. The slope of the function was 0.43 ml. per 100 gm. per second. The linear nature implies that very little mixing occurs between incoming and outgoing plasma, and the single slope supports the thesis that all the albumin is located intravascularly.

EFFECT OF SLOW INFUSION OF GLUCAGON-FREE INSULIN ON HEPATIC OUTPUT OF GLUCOSE IN DOGS WITH PORTACAVAL SHUNTS. *Leonard L. Madison, Burton Combes and William Strickland.* Dept. of Internal Medicine and Surgery, Univ. of Texas Southwestern Medical School, Dallas, Texas.

Endogenous insulin, secreted into the portal circulation, reaches the liver in concentrations greater than that possible for any other tissue. Nevertheless, a direct effect of insulin on hepatic glucose output has not been conclusively demonstrated. This problem was studied by determining the effect of insulin infusion in dogs with complete portacaval shunts, thereby permitting measurement of changes in hepatic rather than splanchnic glucose output. In eight experiments of 90 to 120 minutes duration, hepatic blood flow was determined by the bromsulfalein or radioactive Rose Bengal technics. Arterial and hepatic venous blood specimens were col-

lected at ten-minute intervals during three control periods and during the duration of the insulin infusion. Blood glucose was determined in triplicate by the Somogyi iodometric method. During the first hour of insulin infusion hepatic venous-arterial glucose difference fell significantly ($p = <.001$) from the mean control value of 17.7 mg. per cent to a mean of 8.8 mg. per cent. Concomitantly, hepatic glucose output declined from 42.4 to 23.9 mg. per minute. The decline in arterial glucose from 78.6 to 53.8 mg. per cent could be ascribed entirely to the reduction in hepatic glucose output. These data indicate that in the intact animal endogenous insulin regulates the hepatic glucose output.

STUDIES IN POSTOPERATIVE ILEUS: INTESTINAL MOTILITY AS REFLECTED IN THE PROPULSION OF RADIOPAQUE MATERIALS. *Jasper L. McPhail, James D. Hardy,* J. Harold Conn, Joseph Schor and Sam Robinson.* Dept. of Surgery, V. A. Center, and Univ. of Mississippi Medical Center, Jackson, Miss.

It is the common impression that intestinal motility, especially forward propulsive activity, is largely absent during the hours immediately following major surgery. The purpose of this study was to examine the validity of this impression. The study methods selected were: (1) When the stomach was not entered, 30 cc. of barium sulfate solution was instilled into the stomach per Levin tube. (2) When the stomach was entered, a small radiopaque marker was left in its lumen. A roentgenogram of the abdomen was taken four and twenty-four hours postoperatively to determine the progression.

Fifty patients who had abdominal surgery were studied. Nineteen patients received barium sulfate. In twenty-four hours the barium was in the terminal ileum in four, in the cecum in five, in the ascending colon in one, in the transverse colon in seven and in the sigmoid in two. Bowel sounds were absent in seven patients. Thirty-one patients received the radiopaque markers. In twenty-four hours the markers were in the sigmoid in five cases, in the transverse colon in three, in the ascending colon in one, in the cecum in nine, in the terminal ileum in eleven, in the jejunum in one, and remained in the stomach in only one. Seventeen patients had absent bowel sounds.

It is concluded that propulsive intestinal activity is usually present following major abdominal surgery even with the absence of bowel sounds.

PHARMACOLOGY OF ACETAZOLAMIDE IN MAN, WITH PARTICULAR REFERENCE TO THE CEREBROSPINAL FLUID. *T. H. Maren* and B. Robinson.* Dept. of Pharmacology and Therapeutics, Univ. of Florida College of Medicine, Gainesville, Fla.

Acetazolamide and appropriate placebos were given orally (40 to 80 mg./kg./day) or intravenously (14 to 20 mg./kg.) to sixteen mentally defective children, seven with hydrocephalus and nine without. This and previous studies (*Bull. Johns Hopkins Hosp.*, 95: 199, 1954) show acetazolamide to have the following distribution characteristics in man: well absorbed, excreted unchanged, about 90 per cent bound to plasma protein, secreted by renal tubules, plasma half-life of 100 minutes, sequestration in red cells so that erythrocyte half-life is three days, poorly diffusible into the cerebral spinal fluid, unbound fraction probably distributed through body water except for special compartments. Oral administration of acetazolamide has no immediate effect on cerebral spinal fluid pressure; twenty-four to forty-eight hours after onset of treatment pressure is generally reduced in both "normal subjects" and those with hydrocephalus. The effect lasts while administration of the drug is continued, and appears secondary to slowing of cerebral spinal fluid formation through inhibition of carbonic anhydrase at choroid plexus. Drug action probably affects Cl^- secretion. Intravenous administration of acetazolamide sharply raises cerebral spinal fluid pressure (*Lancet*, 2: 926, 1957) but the effect is transient (thirty minutes) even when plasma concentrations are maintained. Jugular venous pressure is constant. The rise in cerebral spinal fluid pressure appears to be a vascular phenomenon, secondary to inhibition of red cell carbonic anhydrase and carbon dioxide retention, which dilates cerebral vessels, thus increasing intracranial blood flow and volume.

SIMULTANEOUS CR^{51} AND N^{15}-GLYCINE ERYTHROCYTE SURVIVAL TIMES. *John H. Moon, L. D. Abbott, Jr. and G. Watson James, III.** Dept. of Medicine and Biochemistry, Medical College of Virginia, Richmond, Va.

Labeling of normal erythrocytes with radiochromium^{51} shows an apparent half-survival time of 30 $\pm$ 3 days. Using Ashby or N^{15}-glycine

technics, the average erythrocyte survival is about 120 days. By performing simultaneous Ashby and radiochromium^{51} survival times in normal persons, it has been found that the chromium^{51} results can be made to approximate the Ashby data by correcting for a 1 per cent per day elution of the chromium. This correction factor for elution is open to question in the hemolytic anemias.

In this study simultaneous determinations of erythrocyte survival were made in six patients with stable hemolytic states using N^{15}-glycine and radiochromium^{51}. The diagnoses were: sickle cell anemia (four), symptomatic hemolytic anemia (one) and idiopathic hemolytic anemia (one). Since destruction of red cells is a random process in these states, N^{15} data can be handled in the same way as the Cr^{51} data. Five patients had erythrocyte radiochromium^{51} half-lives of 5.5, 6.0, 10.5, 11.2 and 15 days, respectively. The corresponding N^{15} half-lives were 15, 22, 7.3, 15, and 21.5 days. (The data on the other patient required special analysis.) In these patients shortened radiochromium^{51} half-time represented a shortened erythrocyte survival but did not correlate with N^{15} survival data.

THE CELLS AS OSMOMETERS: A CRITICAL REAPPRAISAL USING THE SODIUM AND CHLORIDE SPACE. *William A. Neely.* Dept. of Surgery, Univ. of Mississippi School of Medicine, Jackson, Miss.

Upon the assumption that body cells act as perfect osmometers, Wolf and Conway have developed formulas for fluid shifts and spaces which are fitted well by data obtained from injection of large loads of sodium in experimental animals. However, their data were obtained from animals who were injected with sodium chloride after nephrectomy. In this study eleven male mongrel dogs were prepared by inserting catheters into the urinary bladder and cannulating the femoral artery and vein. The urine was continuously pumped out of the bladders back into a suitable vein. Control thiocyanate space measurements were made as well as plasma sodium, potassium and chloride. Then, 2 gm./kg. of 20 per cent NaCl solution was infused into a femoral vein over a period of seven to ten minutes. After equilibrium, the space and plasma measurements were repeated.

The serum sodium levels increased promptly from normal levels of 144 to 147 mEq./L. to 180 to 210 mEq./L. and remained constant. The serum chloride levels rose from 113 to 123 mEq./L. to 175 to 192 mEq./L. Sodium spaces were found to be 80 $\pm$ 2.8 per cent of total body weight. The chloride space was found to be 58 $\pm$ 1.6 per cent of total body weight.

THE ROLE OF THE SPLEEN IN DEATH FOLLOWING STRANGULATION OBSTRUCTION IN DOGS. *William A. Neely and William O. Barnett.* Dept. of Surgery, Univ. of Mississippi School of Medicine, Jackson, Miss.

Autopsies on dogs dying following intraperitoneal injection of strangulation fluid always showed the presence of reddish fluid and much congestion of the bowel and mesentery. We have set out to assess the relationships of these fluid losses to death. Control thiocyanate space measurements were made on weighed adult mongrel dogs anesthetized with pentobarbital. Control blood volume studies were performed also. After these measurements were completed, 4 cc. of strangulation fluid per kilogram were injected intraperitoneally and the thiocyanate and blood volume measurements repeated at four and eight hours. Another group of dogs were splenectomized and the identical experiment repeated.

RESULTS

	Control	4 Hours	8 Hours
Mean Changes in Blood Volume and Thiocyanate Spaces in Eight Non-Splenectomized Dogs			
Plasma vol....	1.13	.91(P<.02)	.74(P<.001)
Blood vol.....	1.95	2.18(NS)*	1.98(NS)
R.B.C. vol....	.82	1.27(P<.005)	1.24(P<.001)
SCN space...	2.97	2.81(P<.05)	2.51(P<.02)
Mean Changes in Blood Volume and Thiocyanate Spaces in Seven Splenectomized Dogs			
Plasma vol....	1.10	.92(NS)	1.02(NS)
Blood vol.....	2.00	1.82(NS)	2.05(NS)
R.B.C. vol....	.90	.90(NS)	1.03(P<.05)
SCN space...	3.05	2.60(P<.02)	3.00(NS)

* Not significant.

It is concluded that the spleen prolongs survival time by contributing to the red cell mass or by some as yet unknown mechanism.

A METHOD FOR THE MEASUREMENT OF BLOOD FLOW IN ISOLATED SEGMENTS OF SMALL BOWEL AND KID-

NEY IN DOGS. *William A. Neely and M. Don Turner.* Dept. of Surgery, Univ. of Mississippi School of Medicine, Jackson, Miss.

Most methods of measuring blood flow require incision of the vessels and the introduction of suitable devices into the lumen of very small vessels. Other methods depend upon the extraction of some substances by the tissue concerned. There are disadvantages of these methods. In the present study midline incisions were made in adult mongrel dogs. The arteries and veins were dissected out individually leaving the organ connected to the animal only by its vascular supply. A Statham strain gauge transducer was used to suspend the organ in air, free except for its blood supply and venous drainage. While suspended, the efferent vessel was suddenly occluded. Change in weight in grams with time, then, would equal blood flow in cubic centimeters per unit of time.

Mean triplicate measurements of gut segment and renal blood flow, in twelve and eighteen dogs repeating, did not differ significantly. In fourteen dogs the described method correlates well with direct cannulation ($r = 80$) and the means of both methods did not differ significantly.

A simple reproducible method for the measurement of intestinal segmental and renal blood flow is described. The results showed no significant difference between this method and a direct cannulation method. This method correlates well with direct cannulation.

RELATION OF LEUKOCYTE CHANGES AND FEVER FOLLOWING INJECTION OF TYPHOID VACCINE IN NON-TOLERANT AND TOLERANT DOGS. *J. G. Palmer* and J. C. Herion.* Dept. of Medicine, Univ. of North Carolina, Chapel Hill, N. C.

Detailed studies have been made of the relationship between the leukocyte and temperature changes following intravenous injection of typhoid vaccine in dogs. The duration of the leukopenia is approximately equal to the duration of fever, and in non-tolerant animals there is a tendency for a biphasic leukopenia corresponding to the double peak in the febrile response. Leukocytosis appears at the time of defervescence.

When tolerance is established by repeated daily injection of typhoid vaccine the biphasic febrile response is lost with disappearance of the second peak. The period of leukopenia is also shortened and leukocytosis appears sooner. The degree and time of initial leukopenia and fever are unchanged, as is the degree of leukocytosis. Injection of a second dose of vaccine six hours after the first in a non-tolerant animal produces a leukocyte and temperature response resembling that which is seen in tolerant animals. This close relationship of leukopenia to temperature supports the hypothesis that endotoxin fever is mediated by endogenous pyrogen of leukocytes. The resemblance between the response to the second of two closely spaced injections and the response in tolerant animals suggests the possibility that tolerance results from depletion of leukocyte pyrogen or alteration in its release.

SODIUM EXCRETION IN RENAL DISEASE. *Alvin E. Parrish,* Norman C. Kramer and Mary F. Watt.* Dept. of Medicine, George Washington Univ., School of Medicine, Washington, D. C.

Patients with renal disease often show abnormalities in the way in which they handle sodium. This study was undertaken to investigate (1) the relation between insulin and sodium clearance and (2) the effect of sodium loading on the inulin and sodium clearance in patients with renal disease. Inulin and sodium clearances were carried out by the standard methods. Renal needle biopsy specimen or autopsy specimens were obtained in all patients. Sodium loading was performed by infusing rapidly 100 to 300 mEq. of 5 per cent NaCl intravenously.

In fifty patients with various forms of renal disease a significant correlation was found between inulin and sodium clearance ($r = 0.7307$). Such a relation was not observed in fifteen normal patients. In sixteen patients with renal disease sodium loading produced an increase in inulin clearance in only three patients. Sodium clearance rose in ten and filtered sodium rose in seven of the sixteen patients. In three patients the sodium clearance rose even though the inulin clearance fell. These findings suggest that there is a relation between the filtration of sodium and sodium excretion in renal disease, that sodium loading in renal disease results in an increased renal excretion of sodium by (1) an increase in filtered sodium and (2) a decrease in tubular reabsorption of sodium.

CHANGES IN PULMONARY NON-ELASTIC RESISTANCE WITH ACUTE HYPERCAPNIA IN DOGS. *Richard M. Peters,* Thomas B. Barnett and John Parker.* Dept.

of Surgery and Medicine, Univ. of North Carolina School of Medicine, Chapel Hill, N. C.

Previous studies have demonstrated that elevation of arterial pCO_2 is associated with an increase in the amount of pressure required to inflate the lungs. These studies do not clearly indicate whether this increase in resistance is due to a change in non-elastic or elastic resistance of the lung. In the current study, dogs were anesthetized with chloralose, and a tracheostomy and a midline sternotomy were performed. Respiration was maintained with a Starling pump. Flow, volume, and airway pressures were recorded. The dogs were respired on varying concentrations of carbon dioxide and on air. Resistance was calculated at the same flow rate and lung volume for each of the experimental conditions. In ten dogs it was demonstrated that non-elastic resistance increased in a linear fashion as the level of arterial pCO_2 was raised over the range of 25 to 80 mm. Hg. Elastic resistance was unchanged. Atropine given intravenously prevented the increase in airway resistance associated with hypercapnia. The level of non-elastic resistance for any given pCO_2 did not change over a fifteen-minute period.

The clinical implications of this observation are many, and further studies are in progress to determine whether or not similar changes occur with more prolonged periods of hypercapnia.

STUDIES ON THE PATHOGENESIS OF FEVER. THE SPECIES-SPECIFICITY OF ENDOGENOUS SERUM PYROGEN. *Robert G. Petersdorf and Ivan L. Bennett, Jr.** Dept. of Medicine and Pathology, Johns Hopkins Univ. School of Medicine, Baltimore, Md.

Intravenous injection of bacterial endotoxins and influenza viruses in rabbits and dogs is followed by the appearance in the serum of secondary fever-producing substance, endogenous pyrogen, which differs from the material originally administered. Endogenous pyrogen presumably is derived from leukocytes since it is absent in leukopenic animals. The findings that leukocytic exudates are pyrogenic supports this concept. Both endogenous leukocytic and serum pyrogens produce monophasic fever following a brief latent period, are active in tolerant recipients and do not evoke tolerance. Because of these common biological characteristics, the two pyrogens may be identical.

Previous studies demonstrated that leukocytic exudates were pyrogenic only for the species from which they were derived. These observations were extended to endogenous serum pyrogen, and the serums of dogs and rabbits given typhoid vaccine were tested in the homologous and heterologous species. In every instance endogenous pyrogen from canines produced fever in rabbits and vice versa. Endogenous pyrogen obtained by injection of Newcastle disease virus was also pyrogenic for the heterologous species. These results indicate that, in contrast to leukocytic pyrogen, endogenous serum pyrogen is not species specific and suggest that the two fever-producing substances may not be biologically equivalent.

APPLICATIONS OF DIGITAL BIOPSY TO PERIPHERAL VASCULAR INVESTIGATIONS IN MAN, WITH SPECIAL CONSIDERATION TO DERMAL CHROMAFFIN CELLS. *John Phillips, G. E. Burch,** *and R. G. Hibbs.* Dept. of Medicine and Anatomy, Tulane Univ. School of Medicine, New Orleans, La.

The digit is an excellent organ for peripheral vascular investigation since it lends itself easily to functional studies by rheoplethysmography and to structural and correlative studies through biopsy. A safe, simple, quick, relatively painless technic of digital biopsy has been employed approximately 250 times and has provided excellent tissue for investigations into the following aspects of microcirculatory research: (I) *Pathology:* Since the digit is so complex and contains such a sensitive circulatory bed, it appears to reflect vascular manifestations of generalized diseases at an early stage. (II) *Arteriovenous anastomoses (glomus bodies):* These curious structures are found in greatest number in digits. Their anatomy is fairly well known but their function, although probably partly related to temperature regulation, remains to be clarified. (III) *Electronmicroscopy:* Using electronmicroscopy, two distinct types of small vessels were identified. One resembles those of other organs; the other is a specialized type not previously reported. Functional significances of these types are suggested. (IV) *Newly-identified chromaffin cells:* From physiological evidence, locally produced vasoconstrictor agents in skin have been postulated for several years. Using digital biopsy and histochemical technics it was possible to identify chromaffin cells in human skin, a probable source of these vasopressor substances.

COMPARISON OF CLINICAL INFORMATION CONTAINED IN 12-LEAD ELECTROCARDIOGRAM AND IN SCHMITT'S CORRECTED, ORTHOGONAL LEAD SYSTEM. *Hubert V. Pipberger,* Stanley Bialek, Joseph K. Perloff and Harold W. Schnaper.* V. A Hospital, and Dept. of Medicine, Georgetown Univ. Medical Center, Washington, D. C.

Replacement of the conventional electrocardiogram by corrected, orthogonal systems depends upon ample evidence that all information of clinical significance contained in conventional leads can also be recovered by orthogonal systems. To investigate this, 261 patients with electrocardiographic abnormalities were studied by these two recording technics, using conventional methods of interpretation. Special attention was focused on minor electrocardiographic changes. Only scalar recordings were used.

Significant detail encountered in the conventional tracings could definitely not be recognized in the three orthogonal leads in eleven cases. In eight further cases, characteristic features were recognized only in a poorly identifiable form.

A further correlation was performed between the conventional tracings and resolved leads (electronically derived from the three basic leads), using directions similar to the conventional electrode locations. Comparable detail was found in both types of recordings in 260 cases. In one case the reproduction of a T wave abnormality in the resolved leads was questionable.

These data suggest that although three-lead orthogonal systems contain all electrical information derived from conventional electrocardiograms, at the present time resolution and/or refined reading technics of these three leads appear necessary in 7 per cent of the cases to yield the clinical information contained in the standard electrocardiogram.

STUDIES TO DETERMINE THE CAUSE OF HYPOFIBRINOGENEMIA IN PLACENTAL ABRUPTION. *Jack A. Pritchard* and Majorie R. Wright.* Department of Obstetrics and Gynecology, Univ. of Texas Southwestern Medical School, Dallas, Texas.

Commonly proposed to explain the development of hypofibrinogenemia following placental abruption are (1) intravascular coagulation due to thromboplastin entering the maternal circulation or (2) intense fibrinolytic activity. Impressed by the paucity of evidence supporting either concept, studies were initiated to measure the fibrin in the blood clots obtained from the uterine cavity at delivery. These were frozen, thawed, homogenized and centrifuged. The residue was washed repeatedly with saline until colorless, freed of any lipids, and dried. Specimens of blood of which the fibrinogen content was altered widely by adding bovine fibrinogen were clotted with thrombin and similarly treated.

The amounts of insoluble protein recovered from the prepared clots were almost identical with the initial fibrinogen content of the specimens. From both the intrauterine and prepared clots the insoluble protein had a tyrosine content similar to that of fibrinogen and was lysed when incubated with bovine fibrinolysin.

In five cases of placental abruption with hypofibrinogenemia studied to date the recovered protein equalled two-thirds to three-fourths of the fibrinogen calculated to have been lost from the maternal circulation. It is concluded that the major cause of hypofibrinogenemia in placental abruption is coagulation within the uterine cavity.

ANTIMETABOLIC EFFECT OF DL-3,3′,5′ TRIIODOTHYRONINE. *James A. Pittman, John O. Tingley, John R. Nickerson, Robert L. Hayes and S. Richardson Hill, Jr.** Dept. of Medicine and Univ. Hospital, Univ. of Alabama Medical Center, and Medical Service, V. A. Hospital, Birmingham, Ala.

DL-3,3′,5′ triiodothyronine ("reverse trit") was given orally to six patients to evaluate it for inhibition of the calorigenic effect of thyroid hormones. In one euthyroid and one hyperthyroid patient there was no change from control values in the basal metabolic rate or serum cholesterol during administration of reverse trit alone in doses up to 0.68 mg./kg. (single dose of 20 mg./day) at the end of ten days. The twenty-four-hour thyroidal I^{131} uptake in the euthyroid patient diminished from 29.5 per cent to 9.4 per cent. Two hypothyroid patients who were being maintained on desiccated thyroid, 60 and 120 mg. per day, were given reverse trit for four to eight days in doses of 40 to 80 and 80 to 160 mg./day, respectively. The former showed no significant change in basal metabolic rate, but the latter showed a distinct fall from −8 per cent to −32 per cent with post-treatment rise to 0 per cent in fourteen days. Two patients with

myxedema were maintained on 300 μg./day of sodium L-thyroxine and on 100 μg./day of L-3,5,3′ triiodothyronine, respectively. The first patient showed 26 per cent inhibition of metabolic rate at a molar ratio of 322:1 (reverse trit to thyroxine) and 54 per cent at 644:1. The second patient showed 63 per cent inhibition of metabolic rate at a molar ratio of 1100:1 (reverse trit to trit). Per cent inhibition was calculated on the basis of fall in basal metabolic rate from levels on maintenance therapy toward levels on no therapy when reverse trit was given.

It is concluded that DL-3,3′,5′ triiodothyronine can inhibit the stimulating effect of these thyroid hormones on the metabolic rate.

RENAL MECHANISM OF BICARBONATE REABSORPTION. *Floyd C. Rector, Richard M. Portwood, Robert Cade and Donald W. Seldin.** Dept. of Internal Medicine, Univ. of Texas Southwestern Medical School, Dallas, Texas.

Renal HCO_3^- reabsorption was explored in normal subjects during metabolic and respiratory acidosis and alkalosis. HCO_3^- reabsorption (Y) was linearly related to plasma pCO_2 (X), described by the regression equation, $Y = 0.98 + 0.0285 \times (r = 0.81)$. When Diamox® was given during similar acid-base changes, the slope of the regression line was unchanged but the intercept value was lower: $Y = 0.61 + 0.028 \times (r = 0.87)$. This suggests that HCO_3^- reabsorption can be distinguished into two fractions, one independent of C.A. but linearly related to plasma pCO_2, another dependent on C.A. The contribution of the latter is constant over the range of pCO_2 studied, suggesting that C.A. saturates at low pCO_2 (<14 mm. Hg.). Acceleration of HCO_3^- reabsorption during hypercapnea appears to be solely the consequence of the uncatalyzed hydration of CO_2.

During Diamox administration in metabolic acidosis, $[HCO_3^-]$ and HCO_3^- reabsorption are reciprocally related in a Lineweaver-Burk plot. This correlation has been construed as evidence favoring active HCO_3^- reabsorption. Against this interpretation is that different lines are generated in respiratory acid-base changes. Also *in vitro* addition of HCl to buffered HCO_3^- solutions generated similar lines, although neither enzyme nor inhibitor were involved.

It is concluded that HCO_3^- reabsorption is mediated by exchange of H^+ for Na^+, which is dependent on the availability of substrate (pCO_2).

STUDIES ON ORGAN BLOOD FLOW AND METABOLISM DURING EXTRACORPOREAL CIRCULATION. *Keith Reemtsma,* N. Martin Halley and Oscar Creech, Jr.** Dept. of Surgery, Tulane Univ. School of Medicine, New Orleans, La.

The prolonged use of extracorporeal circulation has been accompanied by various complications, and further utilization of this technic is hampered by the lack of knowledge of the physiologic alterations associated with this procedure. This study was undertaken to evaluate changes in the blood flow and oxygen consumption of various organs during cardiopulmonary bypass. A total of forty-eight mongrel dogs was used in this study. Cerebral blood flow was measured with a rotameter. Renal, mesenteric and femoral blood flow were measured by the venous outflow technic. Organ temperatures were monitored, and arterial and venous oxygen content were measured.

Analyses of blood flows demonstrated different responses of various organs to extracorporeal circulation. Cerebral blood flow was closely correlated with arterial pressure, both on and off the pump oxygenator. Renal blood flow fell and mesenteric and femoral flow increased with extracorporeal circulation, and these changes were not closely correlated with arterial pressure. The pattern of oxygen consumption varied with different organs. Cerebral oxygen consumption fell abruptly with extracorporeal circulation, whereas renal oxygen consumption increased. Mesenteric oxygen consumption fell, and the extremity oxygen consumption remained relatively constant despite marked increase in flow.

BACTERIAL ENDOTOXIN IN THE GENESIS OF EXPERIMENTAL CHRONIC PYELONEPHRITIS. *Jay P. Sanford, Betty W. Hunter and Robert E. Windom.* Dept. of Internal Medicine, Univ. of Texas Southwestern Medical School, Dallas, Texas.

In chronic pyelonephritis progressive cellular changes may occur without bacteria being demonstrable in either urine or renal tissue. These progressive changes might be the result of infection with metabolically defective bacteria which are not readily cultured, a response to the breakdown products of the original microorganisms including bacterial endotoxin, or the result of autosensitization evoked by infection.

The localization and fate of immunologically specified viable Escherichia coli (O-111:B-4)

and its breakdown products in the course of experimental hematogenous pyelonephritis in rats was followed using, fluorescent antibody staining, routine histologic and bacteriologic technics. Early, bacteria are uniformly distributed within blood vessels of the kidneys. Within one hour, multiplication is observed and the bacteria invade vessel walls into the interstitial tissue. Organisms multiplying in the interstitial tissue produce microabscesses within eight hours. Bacteria within glomeruli may begin multiplication; however, within eight hours these organisms undergo degeneration and abscesses do not develop. With development of gross abscesses and scarring, morphologically discrete, viable Esch. coli disappear and progressive increase in amorphous endotoxin occurs.

These observations demonstrate that bacterial endotoxin is present in progressively contracting kidneys and may play a role in evoking inflammatory changes as well as predisposing to subsequent localization of bacteria.

REVERSIBLE EFFECTS OF MYOCARDIAL ISCHEMIA IN DOGS. *Nevzat H. Savranoglu, Robert J. Boucek* and Gus. G. Casten.* Dept. of Medicine, Univ. of Miami School of Medicine, and Miami Heart Institute, Miami, Fla.

Ischemia may alter the biochemical and physiological processes of cardiac cells. The purpose of this study was to measure the reversibility of transient myocardial injury by glutamic oxaloacetic transaminase release and by electrocardiographic and histologic examinations. Coronary sinus blood was obtained at five-minute intervals during the initial twenty minutes and after forty minutes of coronary occlusion, and twenty and forty minutes after coronary release. Twenty-one dogs were studied.

Injury potential (electrocardiographic) occurred within three minutes and promptly regressed towards control within minutes following coronary release in all but two dogs. Coronary sinus transaminase (26 ± 9 units) increased significantly in twenty (39 ± 15.3) and forty minutes (57 ± 12). No significant decrease occurred in forty minutes following coronary release (48 ± 11). Eleven hearts were examined histologically, four within two to four hours following coronary occlusion and seven two to six days after. Only one heart revealed evidence of myocardial infarction or injury.

The effects of myocardial ischemia may vary in the rate of reversibility. Enzyme release may occur from the injured myocardium while the electrocardiogram is returning toward the control, and persistence of enzyme elevation for at least eighty minutes does not imply irreversible muscle damage as seen by histologic examination.

USE OF ORAL HYPOGLYCEMIC AGENTS IN THE TREATMENT OF BRITTLE AND POORLY CONTROLLED DIABETES MELLITUS. *John Scoggins, Hooshang Guilak, R. E. Carter, Hunter Montgomery and Harold Dobson.* Metabolic Section, Dept. of Internal Medicine, Baylor Univ. College of Medicine, and Jefferson Davis Hospital, Houston, Texas.

Tolbutamide has been very useful as a drug of convenience in the treatment of mild, obese, adult diabetic patients but it has been virtually useless in the treatment of patients with unstable diabetes and those in poor control receiving large doses of insulin. Chlorpropamide (a sulfonylurea) and phenethyldiguanide (not related to the sulfas) have been used to treat over 100 patients with juvenile diabetes and other forms of poorly controlled diabetes mellitus. In general, these agents have been used in combination with insulin. At least 75 per cent of the patients are still receiving oral therapy, with significant improvement in control, judged by both chemical and clinical criteria. One of the most gratifying results is that it is possible to achieve good chemical control, without subjecting the patient to frequent, recurrent hypoglycemia. It has been possible to use these agents in stress situations, such as infection and surgery. Chlorpropamide has a typical sulfa toxicity pattern, phenethyldiguanide causes minor or major gastrointestinal upset in about 50 per cent of the patients. It is believed that these two agents contribute significantly to improvement of control in "problem" diabetic patients.

A METHOD FOR THE ROENTGENOLOGIC VISUALIZATION OF CORONARY ARTERIES IN DOGS. *William H. Sewell, Wade H. Shuford, Pablo A. Davalos, J. Willis Hurst and H. Stephen Weens.** Dept. of Surgery, Radiology, and Medicine, Emory Univ. School of Medicine, and Grady Memorial Hospital, Atlanta, Ga.

The major branches of the right and left coronary arteries are readily demonstrated by various technics of coronary arteriography.

This project was designed to develop a method in dogs permitting more consistent roentgenologic visualization of the smaller branches of the distal coronary arterial tree. The dogs were anesthetized, paralyzed and artificially ventilated. Electrocardiogram and aortic pressures were monitored. A polyvinyl catheter with side openings was inserted through the carotid artery into the base of the aorta. Cardiac asystole was produced by the injection of 3 to 10 mg. of acetylcholine. Ten cc. of 85 per cent Hypaque® were promptly injected and serial roentgenograms were obtained. Fifty-five arrests were produced in eighteen dogs, and in all instances, the heart spontaneously re-started after fifteen to twenty seconds. P waves sometimes returned before the QRS complex, but there were no other ventricular or auricular arrhythmias.

This study has shown that visualization of the distal coronary arterial tree is dependent upon strict observation of certain technical factors. In fifty consecutive arteriograms the coronary arteries were outlined for several successive branchings, and vessels as small as 0.3 mm. in diameter were consistently filled. This method has been tested in dogs with abnormal hearts and in one instance demonstrated a collateral channel around the apex three days after ligation of the anterior descending branch of the left coronary artery.

BUFFERING MECHANISMS IN HYPOXEMIA AND HYPERCAPNIA AND THEIR RELATIONSHIP TO THE ELECTROENCEPHALOGRAM. *H. O. Sieker* and W. P. Wilson.* Dept. of Medicine and Psychiatry, Duke Univ. School of Medicine, and V. A. Hospital, Durham, N. C.

Serum potassium alterations have been demonstrated in hypoxemia and hypercapnia. It is well recognized that cerebral function may be altered in these situations but it is also remarkable that in chronic pulmonary failure, normal cerebral function is often observed. It was the purpose of this study to elucidate the role of serum potassium alterations as a buffering mechanism in hypoxemia and hypercapnia.

Twenty-six studies were made on twenty-two normal young adult males. The electroencephalogram was correlated with changes in arterial oxygen saturation, pH, carbon dioxide tension, sodium, potassium, glucose and lactic acid. Hypoxemia increased the serum potassium (mean: $3.95 \pm .27$ mEq./L. to $4.12 \pm .24$ mEq./L.) and electroencephalographic alterations were observed in all but two of the subjects at ten minutes. Addition of 2.5 per cent carbon dioxide to the low oxygen gas mixture did not prevent the electroencephalographic changes. Administration of 10 per cent carbon dioxide in air to fasting subjects increased the serum potassium (mean: $3.93 \pm .13$ mEq./L. to $4.27 \pm .07$ mEq./L.) and produced low voltage slowing of the electroencephalogram in all but one subject at five to ten minutes. Hyperglycemia prevented the serum potassium change observed during hypercapnia. All of these subjects showed electroencephalographic changes within two minutes after administration of carbon dioxide, and none were able to remain conscious for ten minutes of carbon dioxide breathing.

The results of this study suggest that small amounts of carbon dioxide do not protect against the cerebral effects of hypoxemia. It is suggested that in hypercapnia, potassium alterations are important as a buffering mechanism to prevent abnormal cerebral electrical activity.

PYRIMIDINE METABOLISM OF NORMAL AND LEUKEMIC HUMAN LEUKOCYTES IN VITRO. *Jacob Shapira and Richard J. Winzler.* V. A. Hospital, Little Rock, Ark., and Univ. of Illinois College of Medicine, Chicago, Ill.

Leukocytes isolated from the blood of normal humans, patients with leukemia, and from normal marrow were incubated *in vitro* in the presence of radioactive precursors of the pyrimidines of the nucleic acids. Significant differences were found in the ability of the various cellular populations to incorporate formate, orotic acid, uracil and thymine into the nucleoprotein fraction. At lower concentrations of these materials, marrow cells preferentially incorporate thymine. Thymine, uracil and orotic acid are incorporated at about the same rate at higher concentrations. The differences in behavior between leukemic cells and normal cells are quite large; for instance, twenty-five times more thymine is incorporated by chronic granulocytic leukemia leukocytes than by normal circulating leukocytes.

The effects of various drugs used in the treatment of leukemia and a number of synthetic pyrimidine analogs were studied. A number of these compounds exerted significant inhibitions on the incorporation of the pyrimidines. Of particular interest was the observation that

5-bromouridine and 5-ethyluridine greatly stimulated the incorporation of uracil into chronic lymphatic leukemia leukocytes. Whereas amethopterin inhibited the incorporation of formate, this same drug stimulated the incorporation of thymine. The results obtained can be interpreted on the basis of known biochemical transformations of the pyrimidines.

FEEDBACK CONTROL OF CHOLESTEROL SYNTHESIS. *Marvin D. Siperstein* and M. Joanne Guest.* Dept. of Internal Medicine, Univ. of Texas Southwestern Medical School, Dallas, Texas.

Feeding diets low in cholesterol, results in increased hepatic cholesterol synthesis, whereas high cholesterol diets markedly decrease cholesterolgenesis. The mechanism of the feedback reaction by which this exogenous cholesterol controls cholesterol synthesis has received little study. The present investigation is an attempt to localize the biochemical site of this regulation of cholesterolgenesis. The reactions of cholesterolgenesis are as follows: acetyl-CoA $\xrightarrow{1}$ acetoacetyl-CoA $\xrightarrow{2}$ β-hydroxy-β-methylglutaryl-CoA $\xrightarrow{3}$ mevalonate $\xrightarrow{4}$ squalene $\xrightarrow{5}$ cholesterol. Feeding a 5 per cent cholesterol diet caused a ten- to one-hundredfold inhibition of acetate-C^{14} incorporation into cholesterol in rat liver slices. Mevalonic-C^{14} incorporation, however, was inhibited only threefold, indicating the location of the major site of inhibition to be at reactions 1, 2 or 3, with perhaps secondary effects in reactions 4 or 5. Further localization of the cholesterol block was shown as follows: Reaction 1 is intact since conversion of acetate-C^{14} to fatty acid involving reaction 1 was normal. Reaction 2 must be unaffected since it is required to convert acetate to β-hydroxybutyrate, and this pathway was normal or increased.

These observations indicate that exogenous cholesterol inhibits cholesterol synthesis primarily by blocking the conversion of β-hydroxy-β-methylglutaryl-CoA to mevalonate. This reaction then becomes the likely site of homeostatic control of cholesterol synthesis in the liver.

INCIDENCE OF INFECTED URINES IN HYPERTENSIVE SUBJECTS. *C. M. Smythe,* C. F. Rivers and R. M. Rosemond.* Medical College of South Carolina, Charleston, S. C.

A group of hypertensive subjects reporting to an outpatient medical clinic for the first time were investigated for the presence of unsuspected, silent, active pyelonephritis. Quantitative urine cultures were made. More than 10^4 organisms per ml. of urine was defined as suspicious infection and more than 10^5 organisms per ml. as significant infection. Of a group of seventy-seven patients, of whom seventy-four were Negro, thirteen (18 per cent) were found to have active pyelonephritis. This group could not be differentiated from the uninfected group of hypertensive subjects by such factors as severity or duration of hypertension, a history of previous toxemia of pregnancy, venereal infection or urinary instrumentation. Intravenous pyelography was also of no help in differentiating the infected from the non-infected hypertensive subject. A group of normotensive subjects drawn from the same clinic, matched for age, sex and race, served as a control for this series. In the control group clean-voided rather than catheterized urine specimens were obtained. Specimens from thirteen of ninety-two patients had a significant number of bacteria present. On rechecking the positive results by catheterization, three of seven subjects have significant infections. If this proportion holds, approximately 6 per cent of the control group will be found to have significant infection. This is the same percentage of medical outpatients found infected by Kass. These data suggest the alternate possibility that hypertension makes the kidney more susceptible to infection, in addition to the well known fact that renal disease predisposes to hypertension. Clean-voided urine specimens obtained from rapidly instructed indigent clinic patients are adequate for bacteriologic testing if the organisms are counted.

EFFECT OF SELECTED BRAIN LESIONS ON PLASMA ELECTROLYTE AND 17–21 HYDROXYCORTICOSTEROID LEVELS. *James P. Spell, Marshall B. Allen, Orlando J. Andy and James D. Hardy.** Dept. of Surgery (and Div. of Neurosurgery), Univ. of Mississippi Medical Center, Jackson, Miss.

The neurosurgical literature contains several references to electrolyte imbalances that appeared to result from brain lesions, particularly of the frontal lobes and not involving the hypothalamus. However, the implications of such reports have been challenged, since they were random and uncontrolled observations, and not substantiated with experimental data. The purpose of the present study was to produce specific frontal and temporal lesions in dogs, and to fol-

low control and postoperative plasma electrolyte and 17–21 hydroxycorticosteroid values. Ten adult dogs were divided into two groups, and frontal or temporal lobe ablation was performed upon each animal. The specificity and adequacy of ablations were later confirmed at autopsy by several cross sections (inadequate ablations were not accepted). Daily levels of plasma sodium, potassium, chlorine, carbon dioxide and non-protein nitrogen were determined; and the mean plasma levels remained constant for at least ten days postoperatively. There was a consistent rise in 17–21 hydroxycorticosteroid values, the rise being twice as great in the frontal lobe group as in the temporal lobe group.

We have thus been unable to produce "neurogenic hypernatremic hyperchloremia" in dogs. A significant rise in plasma 17–21 hydroxycorticosteroids does occur after frontal and temporal lobectomy in dogs.

HOW RELIABLE ARE LIVER FUNCTION TESTS? A REAPPRAISAL IN DOGS. *James P. Spell and James D. Hardy.** Dept. of Surgery, Univ. of Mississippi Medical Center, Jackson, Miss.

The purpose of this study was to evaluate the effects of specific liver lesions in dogs. Thirty mongrel dogs were divided into seven groups, each of which had a specific surgical lesion produced under sterile conditions, e.g., ligation of common bile duct, ligation of hepatic artery, partial hepatectomy or portacaval shunt. The progress of the liver disease in each animal was followed by periodic determinations of serum alkaline phosphatase, serum bilirubin, thymol turbidity, serum phosphorus, cephalin flocculation, and bromsulfalein retention. Animals were sacrificed two to four weeks postoperatively, and autopsy findings were correlated with results of liver function tests. Results of this study were demonstrated by plotting the units of the particular test considered against the time intervals. These graphs revealed the liver function tests to be more helpful in following obstructive disease of the liver than in following vascular lesions of the liver. Of the tests considered, the serum alkaline phosphatase was the most helpful.

A DIRECT READING FLOWMETER FOR EXTRACORPOREAL CIRCUITS. *Merrill P. Spencer,** *A. Robert Cordell, Adam B. Denison, Jr. and Charles A. Barefoot.* Dept. of Physiology and Surgery, Bowman Gray School of Medicine, Winston-Salem, N. C.

A special wide-bore, high-sensitivity, magnet-electrode attachment to the square-wave electromagnetic flowmeter uses two "C" cores whose air gaps abut and create magnetic flux across a narrow plastic channel 2 mm. by 30 mm. in cross section. Gold electrodes are mounted at either end of this section within the magnetic field. The blood passes through a channel 10 cm. in length which changes from a circular cross section to that of the interelectrode channel and back to circular. This change in shape of the cross section is effected by two stainless steel connectors, circular i. d. 9 mm., which maintain a constant cross sectional area. The attachment is capable of carrying blood at 5,000 ml./minute with negligible pressure drop, yet has sufficient sensitivity for small flows. A panel meter is calibrated to read directly in ml./minute and is provided with separate scales for large or small flows. The attachment substituted for any segment of the circuit is cold sterilized, has a smooth channel, is cleaned easily, and has no moving parts. The square-wave electronic circuitry also drives the "surgical probes" used on unopened vessels.

To date the unit has been used for cardiopulmonary bypass procedures in four patients requiring flows of 250 to 5,000 ml./minute and in four dogs with flows of 400 to 1,200 ml./minute. Applied to a phasic recorder it reveals the tremendous flow oscillations caused by present sigmamotor and rotary pump.

GLYCOPROTEIN STUDIES ON THE RHEUMATOID FACTOR. *Willard R. Starnes, Alexander Ulloa and Howard L. Holley.** Metabolic Research Laboratories, V. A. Hospital, and Dept. of Medicine, Medical College of Alabama, Birmingham, Ala.

The term "rheumatoid factor" has been applied to the protein component of serum which is responsible for a group of agglutination and precipitation reactions, some of which are very important as aids in the diagnosis of rheumatoid arthritis. Up to the present time analytical studies have indicated that the rheumatoid factor is a typical 19S gamma globulin with chemical, physical and immunological properties closely akin to known 19S antibodies. The present studies were undertaken to isolate by various procedures the so-called rheumatoid factor. Known positive serums which exhibited

high latex titers were subjected to three different methods for the isolation of the euglobulin fraction. Methods of isolation were: (1) Euglobulin precipitation with hydrochloric acid, (2) Svartz cold agglutination, and (3) continuous electrophoresis. After their isolation the following tests were performed: Paper electrophoresis for proteins and carbohydrates, total protein-bound hexoses, hexosamine and sialic acid. One of the cold agglutination samples was subjected to further isolation studies for the isolation of mucopolysaccharides. The mucopolysaccharides were determined by Dishe's carbazole reaction.

The various euglobulin fractions were found to contain rather large amounts of glycoproteins. If one compares them with gamma globulin, the concentration of total protein-bound hexoses and hexosamines per gram of total protein is markedly elevated. Also a mucopolysaccharide has been partially identified by absorption spectra studies.

SPIROPENTANE: A SURVEY OF ANESTHETIC PROPERTIES. *Frank W. Summers.* Dept. of Anesthesia, Charity Hospital, and Dept. of Surgery, Louisiana State Univ., School of Medicine, New Orleans, La.

Spiropentane is an isomer of pentane which has not been studied for anesthetic activity. The unique bicyclic ring, relatively low molecular weight, and high volatility of spiropentane suggests anesthetic properties.

Only a small quantity was available for testing. Sixteen mice and two dogs were observed under spiropentane anesthesia. Electroencephalogram, electrocardiogram, blood pressure and respiratory exchange were observed in the dogs. Concentrations of spiropentane in the anesthesia circuit were determined by gas chromatography. A concentration of 3 vol. per cent produced anesthesia in one minute and 7 vol. per cent caused respiratory failure within twenty-five minutes. Convulsions, running movements, tachypnea and tachycardia were observed in concentrations producing anesthesia. This preliminary survey of the pharmacological properties in animals indicates that undesirable side actions of spiropentane would preclude its use as a clinically useful anesthetic agent.

PSEUDO-PSEUDOHYPOPARATHYROIDISM AND HEREDITARY MULTIPLE EXOSTOSES. *John N. Todd, III, John F. Nickerson and S. R. Hill, Jr.** Dept. of Medicine and Univ. Hospital, Univ. of Alabama Medical Center, and the Medical Service, V. A. Hospital, Birmingham, Ala.

During the evaluation of three generations of a family with eight members showing the characteristic stigmas of hereditary multiple exostoses, the striking similarity of this disorder to pseudo-pseudohypoparathyroidism became evident. Some of the members of this family not only had multiple exostoses, but also the short, thick set stature, round face and dyschondroplasia involving the metacarpal bones characteristic of pseudo-pseudohypoparathyroidism. The affected members of the family had normal serum calcium, phosphorus, alkaline phosphatase, creatinine and total protein levels. One member of the family, who was extensively studied, had a normal tubular reabsorption of phosphate, an adequate serum phosphate elevation following calcium infusion, and an unsatisfactory phosphaturic response to the intravenous administration of parathyroid hormone (as did a control subject).

In view of the similarity of pseudo-pseudohypoparathyroidism to a spectrum of disorders which includes not only idiopathic hypoparathyroidism and pseudohypoparathyroidism but also myositis ossificans progressiva, familial brachydactyly, epiphyseal dysplasia, and (as demonstrated by this family) hereditary multiple exostoses, a serious question is raised as to the advisability of classifying pseudopseudohypoparathyroidism as a distinct and separate syndrome. A clearer understanding of these disorders might be obtained by considering them as a spectrum of genetically determined bone, calcium and phosphorus disturbances with or without hypoparathyroidism.

SECRETION AND STORAGE OF I^{131} BY THE PAROTID GLAND. *E. J. Towbin and W. H. Perkins.* V. A. Hospital, and Dept. of Medicine, Univ. of Arkansas, School of Medicine, Little Rock, Ark.

In twenty-three technically satisfactory experiments on anesthetized dogs catheters were placed in a parotid vein, femoral artery and parotid duct. Salivary secretion was induced by pilocarpine or electrical stimulation approximately one hour after the intravenous infusion of NaI^{131}. The first specimen of saliva almost always had a much greater iodide concentration than subsequent specimens. In eighteen experiments parotid venous I^{131} concentration rose above the arterial level for the first minute

or two following stimulation. Per milligram, the gland at rest contained five times as much iodide as the gland immediately after stimulation. These results are interpreted to demonstrate that the dog's parotid gland stores iodide during rest and releases it rapidly upon stimulation. Within the first hour the parotid at rest picks up about one-fifth as much iodide, per milligram, as the dog's thyroid.

Preliminary experiments using external counting technics suggest that in man, as in the dog, parotid iodide content falls when salivary secretion is stimulated. Similarities between salivary and thyroid handling of iodide will be discussed as will the similarities between the initial release of iodide and potassium upon stimulation of the parotid.

STUDIES ON SENSITIVITY OF THE RESPIRATORY CENTER. *K. Tripathy, H. O. Sieker* and A. Heyman.** Dept. of Medicine, Duke Univ. School of Medicine, and V. A. Hospital, Durham, N. C.

The sensitivity of the respiratory center to carbon dioxide stimulus is considered to be a function of the prevailing arterial carbon dioxide tension; hypercapnia being associated with a reduction, and hypocapnia with an increased ventilatory response to CO_2 inhalation. The effects of acute changes in arterial pCO_2 on respiratory center sensitivity were studied in six patients with emphysema and three with Cheyne-Stokes respiration in whom CO_2 tension was reduced by administration of aminophylline.

The emphysematous patients with a mean arterial pCO_2 of 60 mm. Hg and oxygen saturation of 91 per cent showed a mean ventilatory response to carbon dioxide stimulus of 0.95 L. of expired air per minute, per mm. Hg pCO_2. Aminophylline administered intravenously produced a fall of pCO_2 to 52 mg. and a rise of O_2 saturation to 93 per cent. The response to CO_2 inhalation remained essentially unchanged with a mean value of .74 L./minute/mm. Hg pCO_2.

The patients with Cheyne-Stokes respiration had a mean arterial pCO_2 of 38 mm. Hg and showed a dramatic response to CO_2 stimulus with a mean value of 2.4 L./minute/mm. Hg pCO_2. Administration of aminophylline abolished the Cheyne-Stokes respiration and increased pulmonary ventilation with resultant lowering of CO_2 tension to 34 mm. Hg. Despite this evidence of stimulation of the respiratory center, the response to CO_2 inhalation remained unchanged. These data indicate that the chemosensitive cells in the nervous system may be influenced by factors other than the prevailing carbon dioxide tension in the blood.

A STUDY OF THE LETHAL MECHANISM IN CLOSED LOOP INTESTINAL OBSTRUCTION. *M. D. Turner, J. B. Grogan and G. W. Truett.* Dept. of Biochemistry, Univ. of Mississippi Medical Center, Jackson, Miss.

A chemical and bacteriological study of the peritoneal fluid collected after experimental production of closed loop obstruction is presented. Closed loop obstruction of the ileum was produced in dogs. At death the peritoneal fluid was collected and subjected to differential centrifugation (65 to 15,500 × G). Toxicity of the supernatant and the centrifugate fractions was determined in normal dogs. The supernatant and centrifugate fractions were then examined for presence of exotoxins and endotoxins. A tributary of the portal vein and a femoral vein were aseptically cannulated. One end of the portal cannula was brought to the outside and the abdomen closed. Control blood samples were obtained. Thirteen dogs received 4 cc./kg. of peritoneal fluid; three dogs received no fluid. Additional samples were obtained at thirty minutes, one and a half, two and a half and four hours after injection. Blood culture plates were prepared and bacterial colonies were counted after twenty-four hours.

Centrifugation data established that the lethal factor contained in strangulation fluid is removed by centrifugation. Significant amounts of exotoxins and endotoxins could not be demonstrated in the peritoneal fluid. Blood cultures after intraperitoneal administration of the fluid were positive within thirty minutes. Control samples were negative.

The data suggest that an overwhelming bacteremia is the lethal mechanism in strangulation obstruction.

DEMONSTRATION IN MAN OF A CORRELATION BETWEEN INSULIN BINDING AND INSULIN ACTION IN PERIPHERAL TISSUES. *Roger H. Unger, Leonard L. Madison, Mary Sue McCall, and Henry Lanz.* V. A. Hospital, and Univ. of Texas Southwestern Medical School, Dallas, Texas.

In vitro studies suggest that insulin binding by certain tissues is a prerequisite for insulin action. The following experiments were designed to determine if a correlation between insulin bind-

ing and insulin action exists in man. Six healthy lean adults were given 0.5 units of insulin I^{131} via the femoral artery after base line blood specimens had been obtained. Insulin binding was estimated by simultaneous external counting of radioactivity over both calves. Insulin action was determined by measuring, iodometrically at two and a half to ten-minute intervals, the arteriovenous glucose difference across each leg for seventy-five minutes.

The ratio of maximal fixed radioactivity on the injected side to the more slowly attained peak of radioactivity contralaterally was 2.6 (range 1.7 to 3.1). This inter-calf difference in fixed radioactivity specifically reflects first-circulation insulin binding since (1) intra-arterial injection of NaI^{131} or albumin I^{131} results in rapid inter-calf equalization of radioactivity; (2) prior intra-arterial injection of unlabeled insulin blocks inter-calf-difference of insulin I^{131}, presumably by presaturating available insulin-binding sites; (3) positive femoral arteriovenous difference in plasma insulin I^{131}. The ratio of increase in glucose uptake on the injected side to that contralaterally was 3.1 (range 2.0 to 3.8). The similarity in these ratios provides the first demonstration in man of a correlation between insulin binding and insulin effect.

THE BLOCKING EFFECT OF ACTH AND THE CATECHOL AMINES ON GLUCOSE UPTAKE BY ADIPOSE TISSUE. *John V. Verner, Jr. and Frank L. Engel.** Dept. of Medicine, Division of Endocrinology, Duke Univ. Medical Center, Durham, N. C.

Adipose tissue has been shown in this laboratory to release non-esterified fatty acids (NEFA) under influence of ACTH, epinephrine and norepinephrine, *in vitro*. Plasma NEFA levels are lowered in normal man by the administration of insulin and glucose and elevated in patients with diabetes mellitus. These data, implying an inverse relationship between fatty acid release and glucose utilization, suggest that fat mobilizing hormones might also affect glucose metabolism. In the present study the effect of these hormones on glucose uptake by adipose tissue was investigated. Fifty to 125 mg. segments of epididymal fat from fasted rats were immersed in Krebs bicarbonate medium containing 100 mg. per cent glucose and 0.2 per cent bovine albumin. After addition of hormone, incubation proceeded in a Dubnoff apparatus at 72 oscillations per minute in air at 36.5°C. Residual and initial glucose concentrations were determined by the Nelson or glucose oxidase method and glucose uptake calculated as mg. per gm. fat/three hours. A representative assay revealed: Control 3.06 $\pm$ 0.134 (S.E.) N = 60; 1 μg. ACTH/ml. 1.47 $\pm$ 0.345; 1 μg. epinephrine/ml. 0.48 $\pm$ 0.251; 1 μg. norepinephrine/ml. 0.59 $\pm$ 0.256.

ACTH and the catechol amines not only inhibited glucose uptake but also blocked the stimulating effect of insulin on this parameter in adipose tissue. These data demonstrate another extra-adrenal action of ACTH and suggest a possible physiological role for the catechol amines as insulin antagonists and inhibitors of peripheral glucose utilization.

THE ANTI-THROMBOPLASTIN EFFECT OF A NEW HEPARINOID-DEXTRAN SULFATE. *Raymond Vickers*, Dept. of Medicine, Univ. of Missouri School of Medicine, Columbia, Mo.

Previous studies have suggested that the anticoagulant action of dextran sulfate differs qualitatively and quantitatively from that of heparin of which it is an analogue. We have reported the greater ability of platelets treated with this drug to withstand destruction, a condition noted in hemophilia. Studies have therefore been made of these platelets in thromboplastin generation systems with and without this drug. It was found that there was an abnormal release of platelet factor 3, associated with a delay in viscous metamorphosis. This was dependent on the duration of exposure. Fat solvents, ultrasonic radiation, and freezing were capable of restoring the platelet function to normal, but thrombin was not. That this was not an effect of platelet cofactor 1 inhibition was suggested by the similar behaviour of platelets from patients with plasma thromboplastin component and plasma thromboplastin antecedent, and the inability of ether-extracted platelet-free hemophiliac plasma to correct the defect. (Serotonin and factor 1 release occurred abnormally rapidly; and factor 2 could not be studied in an antithrombin system.)

It is suggested from these studies that there is a molecular coating of the platelets by dextran sulfate. This may be of significance in the agglutination characteristics of platelets preserved by the drug.

SOME DIFFERENCES BETWEEN ESSENTIAL HYPERTENSION AND NOREPINEPHRINE HYPERTENSION.

John M. Wallace. Dept. of Medicine, Duke Univ. Medical Center, and Durham V. A. Hospital, Durham, N. C.

Norepinephrine is the normal sympathetic vasoconstrictor agent. When infused into healthy persons it produces a high blood pressure which is similar in many respects to essential hypertension. In the course of a study comparing vascular reflex responses of hypertensive patients with those of norepinephrine-infused normal subjects, the following differences between essential and norepinephrine hypertension have been noted: (1) Normal non-respiratory vasomotor blood pressure fluctuations are present in most hypertensive subjects but are abolished by the administration of norepinephrine. Norepinephrine produces a flattened intra-arterial tracing at a high level whereas TEAC flattens the tracing at a low level; (2) normal arterial reactions to the Valsalva maneuver are not changed by essential hypertension but are markedly altered by norepinephrine, which abolishes the hypotensive and overshoot phases causing a heart failure-like response; (3) peripheral venous constriction is not present in essential hypertension but is pronounced with norepinephrine. This, rather than an arterial effect, probably explains the differences in Valsalva responses.

If a circulating vasoconstrictor of renal or other origin is important in hypertension, it appears that it must selectively constrict arteries and not veins, and that it must not depress normal resting blood pressure variability which is probably mediated by the sympathetic nervous system.

A CLARIFICATION OF THE HEMODYNAMIC CHANGES IN CIRRHOSIS OF THE LIVER. *W. Dean Warren and William H. Muller, Jr.** Dept. of Surgery, Univ. of Virginia School of Medicine, Charlottesville, Va.

Hemodynamic deviations were studied in patients undergoing portacaval shunt, utilizing intrahepatic portal vein catheterization. The portal vein and hepatic artery were occluded at operation before and after the shunt procedure, and wedged portal vein pressures were measured. Postoperatively, the free and wedged portal pressures were restudied by catheterizing a side-to-side portacaval shunt via the saphenous vein and inferior vena cava. Portal vein oxygen saturations were obtained before and after operation.

These data indicated that the essential hemodynamic pathology in cirrhosis of the liver is outflow obstruction. With moderate changes, the portal vein still supplies a significant amount of the hepatic blood flow but in severe cirrhosis the portal vein may change entirely to an outflow tract. Following side-to-side portacaval shunts, blood flow in the portal vein was retrograde and oxygen saturation studies after shunts indicated utilization of the blood by the hepatic parenchyma. Repeat catheterization studies revealed a greater decrease in hepatic sinusoidal pressure than would be expected with an end-to-side anastomosis.

These studies failed to demonstrate the importance of intrahepatic Eck fistulas or arteriovenous communications in the pathogenesis of cirrhosis. The superiority of the side-to-side shunt is based on the increased venous outflow bed, decreased resistance to arterial flow and lowered intrahepatic pressure.

CEREBRAL VASOCONSTRICTOR RESPONSE TO REDUCTION IN BLOOD CARBON DIOXIDE. *Albert J. Wasserman and John L. Patterson, Jr.** Dept. of Medicine, Medical College of Virginia, Richmond, Va.

Information on the cerebral vasoconstrictor threshold to reduction in arterial CO_2 tension is essential in defining the role of CO_2 in control of the circulation of the brain. As anticipated from earlier work, nitrous oxide studies in three normal subjects showed cerebral oxygen consumption ($CMRO_2$) unchanged by mild hyperventilation. With $CMRO_2$ constant, cerebral blood flow (CBF) varies as the reciprocal of the cerebral arteriovenous O_2 difference. This function, $1/(A\text{-}V)O_2$, was measured by continuous oximetry in sixteen complete experiments on eight normal human volunteer subjects and correlated with arterial PCO_2 (Riley method). Cerebral vasoconstriction was initiated by 1 to 2 mm. Hg reductions in arterial PCO_2, and a 5 mm. Hg fall in PCO_2 produced a 14 per cent decrease in CBF. A 26 per cent (nearly maximal) reduction in CBF was produced by a decrease in PCO_2 of 13 mm. Hg. Only a small increase in alveolar ventilation is required to produce a 5 mm. Hg fall in arterial PCO_2.

These studies demonstrate that a small reduction in arterial PCO_2 produces substantial

cerebral vasoconstriction. Fortunately, opposing protective mechanisms prevent intense vasoconstriction during hyperventilation, even of marked degree. The sensitivity of the response demonstrated in these studies suggests the occurrence of significant cerebral vasoconstriction in a variety of clinical states.

METABOLIC OBSERVATIONS ON THE EFFECT OF VARIED CALORIC AND PROTEIN INTAKE ON THE ANABOLIC EFFECTS OF NOR ISO-ANDROSTERONE (NILEVAR®) FOLLOWING PULMONARY RESECTIONS. *Watts R. Webb and Hector S. Howard.* Dept. of Surgery, Univ. of Mississippi School of Medicine, Jackson, Miss., and Mississippi State Sanatorium, Sanatorium, Miss.

Metabolic balance studies have been performed on male patients undergoing pulmonary resections for tuberculosis to evaluate varying caloric and nitrogen intakes and the "anabolic" steroid, nor-iso-androsterone.

The following regimens were used with and without Nilevar, each on at least three patients: (1) 1,100 calories, no protein; (2) 1,100 calories, 84 gm. of protein; (3) 2,500 calories, no protein; (4) 2,500 calories, 84 gm. of protein. During the first three postoperative days calories were supplied by intravenously administered glucose and fat (Lipomul®), and nitrogen by Amigen.®

In the patients on the low calorie, no nitrogen regimen, the nitrogen loss averaged 10 gm. per day during the first three postoperative days, and with Nilevar about 8 gm. per day. The patients on the low calorie diet receiving adequate nitrogen lost only 4 gm. daily. Nilevar did not reduce this loss. Patients on high calorie, adequate nitrogen intake maintained their weight and achieved nitrogen balance. The patients on the high calorie, no nitrogen diet lost about 7 gm. daily, which was unchanged by Nilevar. A non-operated group on adequate oral calories and protein showed no change with Nilevar. These studies suggest Nilevar may be mildly anabolic with sub-basal diets but is not as effective as additional calories or protein following major pulmonary surgery.

ENERGY METABOLISM OF THE TRANSPLANTED REFRIGERATED HEART. *Watts R. Webb and Sae S. Lee.* Dept. of Surgery, Univ. of Mississippi Medical Center, Jackson, Miss.

The metabolic requirements of transplanted hearts were determined to evaluate the effects of anoxia and short term periods of refrigeration. Hearts from small dogs were transplanted into the necks of larger dogs so that coronary flow could be measured. Oxygen, carbon dioxide, pyruvate, lactate and glucose metabolic rates were determined for hearts immediately transplanted and compared with those refrigerated for six to eight hours at 4°c. before transplantation.

Oxygen consumption of the heart pumping only its coronary flow averaged about 8 cc./100 gm. of left ventricle, and increased several fold, as did metabolite utilization with increasing work or heart rate. Coronary flow increased from about 125 cc. to around 400 cc./minute. Immediately after restoration of function the refrigerated hearts had higher coronary flows, glucose and oxygen utilization. Lactate and pyruvate were in negative balance, but gradually reverted toward normal. The clinical status and the metabolite utilization of the refrigerated heart were improved by riboflavin and thiamin infusions. The metabolic state of both the anoxic and the refrigerated hearts gradually returned to approximately that of the normal heart *in situ*.

EFFECT OF RESPIRATORY PRESSURES ON PULMONARY PRESSURES (INCLUDING PULMONARY ARTERIAL AND VENOUS WEDGE PRESSURES) IN THE OPEN AND CLOSED CHEST OF THE INTACT ANIMAL. *Watts R. Webb and Josef R. Smith.* Dept. of Surgery and Medicine, Univ. of Mississippi School of Medicine, Jackson, Miss.

To study the circulatory effects of respiratory pressures, continuous pressures were recorded in dogs from the pulmonary artery, pulmonary arterial wedge, pulmonary venous wedge, left atrium, trachea, and pleural space with the chest both open and closed. The pulmonary arterial wedge pressure was found to parallel, in general, the left atrial and the venous wedge the arterial pressures, at moderate positive or negative pressures. With higher positive pressure the arterial wedge more closely approximated the arterial and the venous wedge the left atrial pressures.

With the chest open or closed, gentle positive pressure initially resulted in a fall in the pulmonary arterial wedge pressure, reflecting straightening and dilatation of the capillary bed. With higher positive pressures, the pulmonary artery wedge rises exponentially to approximately the pulmonary arterial pressures, and the venous wedge pressure falls on plateaus, reflecting mechanical compression of the pul-

monary capillary bed by distended alveoli. The pressure level at which this block occurred was variable, but usually has been within the range of ventilatory pressures utilized in clinical anesthesia.

Derived curves from varying levels of positive-negative, and positive pressures will be presented to support the concept that increasing pressure initially straightens and dilates the vascular bed, but later causes complete capillary obstruction.

OPERATIVE OBSERVATIONS FROM FORMULARY (PULSE PRESSURE) CALCULATIONS OF CARDIAC OUTPUT AND TOTAL PERIPHERAL RESISTANCE. *Watts R. Webb and J. L. Wofford.* Dept. of Surgery, Univ. of Mississippi School of Medicine, Jackson, Miss., and Mississippi State Sanatorium, Sanatorium, Miss.

Calculations, using the formulas of Starr for determining cardiac output and peripheral resistance from blood pressure, and pulse recordings during operations and emergencies have provided a means for interpreting from moment to moment the patient's responses to surgical manipulations, trauma and various drugs. For example, bucking respirations are found to diminish cardiac output to as low as one-third of normal, and raise the total peripheral resistance eightfold. Administration of succinyl choline chloride in large doses affects neither, but the act of tracheal intubation, nonetheless, may have profound effects on both.

Careful bimanual positive pressure respiration, like positive-negative respiration, causes little change, while inept positive pressure may markedly diminish cardiac output without strikingly altering the blood pressure according to usual clinical standards. Temporary bronchial occlusion has little effect, as does pulmonary artery occlusion, although in advanced emphysema a fall in cardiac output may occur. Rough turning of a patient immediately lowers the peripheral resistance and later the cardiac output by venous pooling.

The etiology of a developing hypo- or hypertension can be classified as produced by alterations of peripheral resistance, heart rate (vagal effect), oligemia, or postarteriolar pooling to provide the basis for a more rational approach to clinical therapy.

EFFECT OF ALTERATIONS IN POTASSIUM ON DIGITALIS-INDUCED VOMITING IN CATS. *James W. Woods, Ernest Craige and Robert W. Winters.** Dept. of Medicine, Univ. of North Carolina School of Medicine, Chapel Hill, N. C.

The effectiveness of potassium salts in abolishing cardiac arrhythmias secondary to digitalis is well known. It has been suggested that potassium may eliminate the extracardiac symptoms of overdosage. A study was designed, therefore, to determine whether or not pretreatment with potassium would protect the cat against an emetic dose of digitalis. In a preliminary study, 0.10 to 0.14 mg./kg. of desacetyl-lanatoside C was found regularly to produce vomiting in all animals after an average interval of thirty-six minutes. Thirty-two young adult cats were then randomly divided into four groups. Animals in groups II and IV were pretreated with an intraperitoneal injection of 2 to 3 mEq./kg. of KCl in 25 ml. of normal saline solution one hour prior to administration of lanatoside C. The comparable control groups received either no treatment (group I) or 25 ml. of normal saline solution intraperitoneally (group III). Differences between the mean emetic response time of control versus potassium-treated groups were not significant at a challenge dose of 0.14 mg./kg., but were highly significant at a dose of 0.10 mg./kg. The results of these experiments suggest that pretreatment with potassium partially protects the cat from digitalis-induced emesis, unless the challenge dose is overwhelming.

Case Reports

Thrombotic Thrombocytopenic Purpura of Long Duration*

SEAMUS F. CAHALANE, M.B., B.CH., ROBERT C. HORN, JR., M.D.
Dublin, Ireland *Detroit, Michigan*

REPORTS have appeared in the literature on more than one hundred cases of thrombotic thrombocytopenic purpura. Of 116 case reports reviewed by the authors all but four of the patients described have died, ninety-eight succumbing to the rapid febrile illness within a matter of weeks. In fifteen patients the fatal illness lasted longer than three months, the longest survival being sixteen years, while other patients were still alive for periods varying from three months to eight years after the onset of the disease. It is the purpose of this paper to add another case of prolonged survival and to analyze the cases from the literature in which the disease has run a prolonged course.

When Baehr [*1*] and his associates first delineated the pathology of thrombotic thrombocytopenic purpura in 1935 (eleven years after the first and only other case of the disease had been described by Moschcowitz [*2*]), one of the four cases reported may well have represented a protracted form of the illness, inasmuch as headache, malaise and weight loss occurred as prodromal events over a six-month period, with hematuria supervening during the final six weeks before the onset of the clinically typical illness. This case represents the first recourse to splenectomy in this disease (in the belief that the patient was suffering from idiopathic thrombocytopenic purpura) but the patient did not survive the surgical procedure. The diagnostic lesions of thrombotic thrombocytopenic purpura were systemically distributed at autopsy and non-bacterial verrucal endocarditis was also encountered.

The case of Brown and Norman [*3*] reported in 1946 was characterized by remissions and relapses over a five-year period in a young white male during which time there were episodes of arthritis, swelling of the legs, fever, abdominal pain and positive serological tests for syphilis. Thrombocytopenia, fluctuating fever and anemia were other clinical manifestations. The positive serological test was in all likelihood an instance of false positive reaction and the positive cephalin flocculation tests reflected an abnormality of serum proteins. Jaundice was absent throughout the illness but petechial hemorrhages appeared late in the course. Autopsy findings included characteristic disseminated vascular lesions. The case was complicated terminally by sepsis, bacterial endocarditis of the mitral and aortic valves, abscesses throughout the body, and thrombosis of larger vessels.

In 1947 Engel [*4*] and his associates reported a case of three months' duration. The onset of illness was associated with a sensitivity reaction to sulfonamides, and the clinical course was characterized by petechiae, fever and transitory involvement of the central nervous system. A remission of one month followed splenectomy.

Beigelman's [*5*] first case concerns a fifty-four year old woman who was treated over a period of eleven years for a variety of complaints, including arthritis, swelling of the legs and feet, dyspnea, dizziness and malaise. She also received antisyphilitic therapy and exhibited a mild anemia. The final illness of three months' duration followed treatment of a suspected urinary tract infection with sulfonamides. This was characterized by fever with progressive anemia and thrombocytopenia without purpura, jaundice or central nervous system involvement. The bone marrow was hypoplastic. At autopsy "platelet thrombi" were found in the heart and the kidneys. Lesions suggestive of lupus erythematosus in the form of "onion skinning" and "wire loops" were encountered in the spleen and kidneys, respectively.

Although these cases appear indeed to have been instances of thrombotic thrombocytopenic purpura of prolonged duration it was Meacham [*6*] and his co-workers who described the first well authenticated case of chronicity and remission. The initial illness was characterized by fever, hemolytic anemia and

* From the Department of Laboratories, Henry Ford Hospital, Detroit, Michigan.

thrombocytopenia. A complete remission of more than two years' duration followed splenectomy but then mental deterioration ensued, leading eventually to coma. A second, brief but nonetheless striking remission was obtained, coincident with the exhibition of ACTH therapy. At autopsy hemorrhage was a pronounced gross feature and thrombotic occlusion of larger vessels was found in the cerebrum, lungs and small bowel. It is noteworthy that there were gross infarcts in the spleen which had been removed three years prior to death. Both leaves of the mitral valve were the seat of non-bacterial vegetations, and typical vascular occlusive lesions were widespread.

Symmers and Barrowcliff [*7*] described a case in 1951 of a man whose illness lasted three months but in whom gross hematuria and albuminuria had developed four months previously. Clinically this case was characterized by intermittent fever, transitory mental disorder, azotemia and anemia. A remission sufficiently complete to allow his discharge occurred but he relapsed promptly and was readmitted to the hospital one week later. He died soon thereafter. The characteristic lesions were found in the capillaries, arterioles and occasional venules throughout the body. Changes reminiscent of wire loops were seen in the kidneys. There is no description of endocardial vegetations.

In 1951 Gardner [*8*] and his associates described a case of unusual interest in a twenty-four year old woman who, at eight years of age, had an illness characterized by anemia, jaundice, a palpable spleen and reticulocytosis, from which she recovered spontaneously. Jaundice reappeared briefly at the age of nineteen. Her final illness was febrile and was accompanied by icterus, thrombophlebitis and pulmonary infarction. Hemolytic anemia, thromboyctopenia, a positive Coombs' test and a rather elusive hemolysin in addition to an elevated gamma globulin were the significant laboratory findings. ACTH therapy led to abatement of fever, cessation of thrombophlebitic episodes, correction of the globulin level and decrease in the antibody titer. All of these features promptly recurred on withdrawal of the drug and neurologic disturbance supervened. Splenectomy was performed on the forty-third day of her illness and brought about a nine months' remission with disappearance of the hemolysin, reversal to negative results of the Coombs' test and return to normal of the serum globulin. Finally, purpura accompanied by mental deterioration set in, although the peripheral blood values and the Coombs' test remained normal. The diagnosis was made only at autopsy.

Gendel [*9*], in 1952, reported a case of a thirty year old man who had had recurrent thrombophlebitis and ulceration of the legs for seven years and in whom anemia, fever and a butterfly rash developed with mild transient central nervous system changes four to five months before death. He was sensitive to penicillin. The laboratory findings were those of a hemolytic anemia, positive serological tests for syphilis and disordered serum proteins. Results of an L.E. test were negative. The platelet count remained normal except for a slight terminal decrease. At autopsy, in addition to the characteristic lesions of thrombotic thrombocytopenic purpura, there were enlargement of the liver and spleen and non-bacterial verrucous vegetations of the mitral valve.

Case I of Monroe and Strauss [*10*] (1953) is one of five months' duration in a twenty year old white man, the onset of whose illness coincided with the administration of sulfonamides in the treatment of gonorrhea. Hematuria, purpura and central nervous system changes were described but no blood count or platelet count was made. At autopsy the characteristic arteriolar and capillary changes were widespread. Other findings included non-bacterial verrucous endocarditis of the mitral valve, extensive adrenal hemorrhage and "acute hemorrhagic proliferative glomerulonephritis."

Vassar and Spain [*11*] in 1953 published clinical and pathologic observations on seven patients who died of thrombotic thrombocytopenic purpura. Two of these cases appear to represent intermittent or chronic forms of the illness (Cases I and VII). Their first case, a twenty-one year old white man, had an illness lasting nine months; an unexplained albuminuria had been present for nine months before that. The onset of acute illness was triggered by an upper respiratory infection and the clinical course was from then on typical of the acute disease. The illness in Case VII lasted three months and there was terminal central nervous system involvement. The laboratory findings in each case were compatible with the diagnosis of thrombotic thrombocytopenic purpura. This was confirmed by the finding of typical vascular lesions at autopsy. In addition there were verrucous endocardial vegetations in both cases. In the first case the vegetations were septic as the patient had a generalized septicemia resulting from an abscess of the buttock, but the lesions in the second case, which involved the mitral valve, were non-bacterial. Non-bacterial verrucous endocarditis occurred in a third case in this series in a patient whose illness had lasted six weeks.

The case presented by Popper [*12*] in 1954 at a clinical pathologic conference at Cook County Hospital is seldom referred to in the literature but deserves more widespread attention. A forty-one year old Negro man with a history of treated syphilis had noticed easy bruising over a period of eight years and had experienced transient bizarre episodes referable to the central nervous system over most of this same

period. He underwent splenectomy after fifteen days of therapy with ACTH-cortisone but died postoperatively within twelve hours. The autopsy findings included petechial hemorrhages in the brain, encephalomalacia, generalized lymphadenopathy, adrenal cortical necrosis, left pleural effusion, Laennec's cirrhosis, testicular atrophy and pancreatitis, in addition to the characteristic vascular lesions throughout the body. The heart was not described and so presumably there were no endocardial lesions.

Fisher and Creed [*13*] in 1955 described the illness of a thirty year old white man who had exhibited a marked anemia and leukocytosis five years previously and a thrombocytopenia of 150,000 per cu. mm. four years previously. Eight years prior to this the patient had sporadic attacks of unexplained muscular fibrillations over many months. The terminal illness lasted three months and was characterized by intermittent episodes of mental and neurologic disturbance, petechial hemorrhages and enlargement of the spleen. Laboratory findings of marked anemia, leukocytosis, eosinophilia, thrombocytopenia, albuminuria and abnormal serum proteins were reported. At autopsy the vascular lesions of thrombotic thrombocytopenic purpura were present in most of the viscera, and mural thrombi were found in both left and right ventricles. The spleen, which was greatly enlarged, contained several infarcts.

A case of well established prolonged course was reported by Baez-Villasenor and Ambrosius [*14*] in 1957. This was an illness of eight years' duration characterized by intermittent attacks of purpura, anemia and thrombocytopenia, occasionally accompanied by jaundice but never by fever. Neuropsychiatric manifestations were not present until the final episode and then they were typically bizarre and transient. The laboratory findings included thrombocytopenia, spherocytic anemia, elevated fecal urobilinogen, albuminuria and a positive Coombs' test. At autopsy widespread vascular occlusions were accompanied by purpura of the skin, myocardium, adrenals and intestinal mucosa.

During 1957 four cases of unusual interest were reported. Three of these are well established cases in which the patients were still living at the time of reporting, following splenectomy, and in the fourth case a clinically typical episode, unconfirmed histologically, was followed by complete remission. Siegel's [*15*] case represents an instance of striking clinical response following splenectomy in a twenty-two year old woman who had a fully developed syndrome of thrombotic thrombocytopenic purpura including fever, jaundice, purpura and mental and neurologic disturbances. Thrombocytopenia was severe, the serum proteins were abnormal. Characteristic lesions were found in the surgically removed spleen. Following surgery the previously prolonged bleeding time became normal. The platelets and reticulocytes reached normal proportions five days postoperatively. A puzzling feature of this unusual case is the finding of positive results of an L.E. test nine months following splenectomy. This patient was still alive and well thirty-two months after surgery.

The patient of Shapiro and associates [*16*] is still living thirty-two months after splenectomy, in complete remission. The clinical and laboratory findings of purpura, fever, jaundice, hemolytic anemia and thrombocytopenia are supported by the findings of characteristic vascular changes in the spleen and lymph nodes.

The case of Nussbaum and Dameshek [*17*] is one of spontaneous remission in a thirty year old white woman suffering from meningococcemia and an illness clinically characteristic of acute thrombotic thrombocytopenia purpura in which the usual diagnostic conditions of hemolytic anemia, thrombocytopenia, fever and severe fluctuating signs in the central nervous system were fulfilled. She received sulfonamides early in her illness and prior to the development of these latter signs. This illness lasted approximately three months, the only residuum being a mild anemia. Unfortunately an attempt to substantiate the diagnosis by histologic examination of bone marrow sections was unavailing. Treatment in this case consisted of antibiotics, whole blood, and ACTH administered intravenously.

Rodriguez and his associates [*18*] reported another case of dramatic recovery following splenectomy in acute thrombotic thrombocytopenic purpura. Clinical and laboratory remission had been sustained for twelve months at the time of publication. Their patient was a thirty-six year old woman who presented with purpura, aphasia and severe hemolytic anemia as well as thrombocytopenia. Recovery commenced on the first postoperative day.

Scalfi and his associates [*19*] reported yet another case of chronic or intermittent course. This patient was a thirty year old woman who in 1952 had thrombophlebitis of a lower limb with involvement of the toes suggesting Raynaud's syndrome. An attack simulating an acute surgical condition of the abdomen occurred in August 1954 and was followed by jaundice. She recovered in eight days. A similar episode occurred three to four months later and again in September 1955. On this occasion there were accompanying fever, hypochromic anemia and leukocytosis. Following a further brief remission she again became febrile, and ecchymoses, marked vascular insufficiency of the affected foot and evidence of mental disturbance developed. The diagnosis was established on biopsy of skin and muscle and she was given corticoids. She died at the end of October 1955.

In addition to the foregoing cases there are instances in the literature in which acute thrombotic thrombocytopenic purpura has been presaged over a prolonged period by varied and often vague symptoms. Such a case is the second patient of Fitzgerald and co-workers [*20*], a twenty-seven year old woman in whom urticaria developed soon after receiving sulfonamide therapy for infected gums. (It is likely that she had been similarly treated for a Bartholin's abscess and for gonorrhea one and three years previously). Occasional recurrence of the rash together with vague complaints of a generalized nature marked the subsequent ten months before the typical cataclysmic events supervened and she died within a week.

Within the past three years papers have appeared in the Swiss [*21*], English [*22*] and American [*23*] literature describing an unusual syndrome in older infants in which there have been hemolytic anemia, thrombocytopenic purpura and severe renal disease. Spontaneous recovery with or without recurrence has been the general outcome, although fatalities and lesions typical of thrombotic thrombocytopenic purpura have been found at autopsy in some of the latter. These cases are not included within the present review as the published clinical and pathologic data leave some doubt as to their exact identification with this disease.

CASE REPORT

A. J. (No. 430848), a forty-one year old white housewife, was admitted to Henry Ford Hospital for the last time on May 23, 1956, suffering from exacerbation of a lengthy intermittent illness.

During her first pregnancy at the age of twenty-three a positive serologic test for syphilis was discovered and she received intermittent treatment for two years. Since that time the serological test has been variously positive and negative, although the cerebrospinal fluid serological reaction has been constantly negative. During a subsequent pregnancy at age twenty-five the patient suffered from toxemia and had convulsions in the postpartum period.

She was first seen at Henry Ford Hospital at the age of twenty-nine complaining of recurrent dizzy spells and of excessive gain in weight. The physical and laboratory findings, with the exception of positive serologic tests, were normal. Over the ensuing seven years she was treated as an outpatient for psychomotor epilepsy with little variation in complaints or physical findings. Several blood and urine examinations were negative during this time. A biopsy of a breast nodule at the age of thirty-eight (August 1953) was diagnosed as fibrocystic disease and at this time an anemia was first noted. (Review of this tissue three years later, following the patient's death showed the presence of so-called "platelet thrombi.") (Fig. 1.) Following surgery, blurring of vision in the right eye occurred and became progressively more severe. Funduscopic examination showed occlusion of the inferior nasal and macular vessels. The significant laboratory findings at this time were: hemoglobin, 11.3 gm. per cent; white blood cells, 8,200 per cu. mm.; polymorphonuclear leukocytes, 81 per cent; lymphocytes, 19 per cent, Kline test 4-plus, Kahn test 4-plus.

In November 1953 transient numbness of the right hand occurred and on one occasion there was loss of consciousness followed by confusion. The patient was readmitted to the hospital in December 1953, at which time physical examination showed that she was withdrawn, non-communicative and somewhat resistant; the temperature was 99°F., pulse 88, and blood pressure 120/70 mm. Hg. The skin was sallow but not jaundiced. There was no purpura. Small shotty cervical and inguinal lymph nodes were felt, but none of the abdominal viscera was palpable. The lungs were normal. The only positive physical findings were a presystolic murmur at the apex and weakness of the right hand and right side of the face.

The patient had a stormy course over the next four months. Late in December there were several seizures of the right hand and head, each lasting from ten to twenty seconds. The neurological findings fluctuated. They included mixed aphasia, echolalia, weakness in the right hand, incontinence of feces and urine, and a left-sided Babinski sign on one occasion. There was further retinal occlusion but no papilledema. Thrombophlebitis developed in the right leg and the temperature was elevated to 104°F. Heparin and later dicumarol were administered, and these were maintained following the patient's discharge after four months.

Laboratory examination revealed the following: red blood cells, 3,600,000 per cu. mm.; hemoglobin, 9.6 gm. per cent; white blood cells, 6,700 per cu. mm.; polymorphonuclear leukocytes, 81 per cent; platelets, 70,000 per cu. mm.; reticulocytes, 1.8 per cent. The serum bilirubin, indirect, was 0.26 mg. per cent; direct, negative. The Coombs' test was negative, blood group O Rh plus. The serum nonprotein nitrogen was 40 mg. per cent, serum albumin, 3.8 gm. per cent; serum globulin, 2.5 gm. per cent; cephalin cholesterol reaction, 4-plus; thymol turbidity, 3 units; thymol flocculations, negative. The erythrocyte sedimentation rate was 34 mm. Examination of the urine disclosed a trace of albumin, occasional granular casts and occasional red blood cells. An L.E. test was negative. The Kline test was plus, Kahn plus, Eagle plus, Kolmer 44440. The Treponema pallidum immobilization test was negative. The cerebrospinal fluid was clear, opening pressure 110, protein 25 mg. per cent, no cells. The electroencephalogram showed changes consistent with an expanding intracranial lesion involving the left hemisphere, maximal in the temporal region. Ventriculograms showed enlargement of the third and lateral ventricles. X-ray film of the chest showed increased left pulmonary markings.

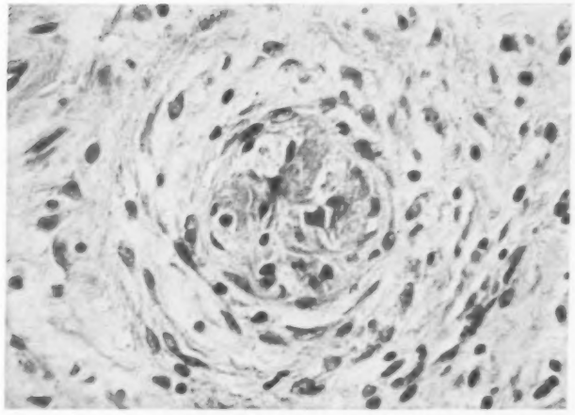


FIG. 1. Organized thrombotic material in capillary of breast tissue removed surgically three years before death. Hematoxylin and eosin, original magnification × 780.

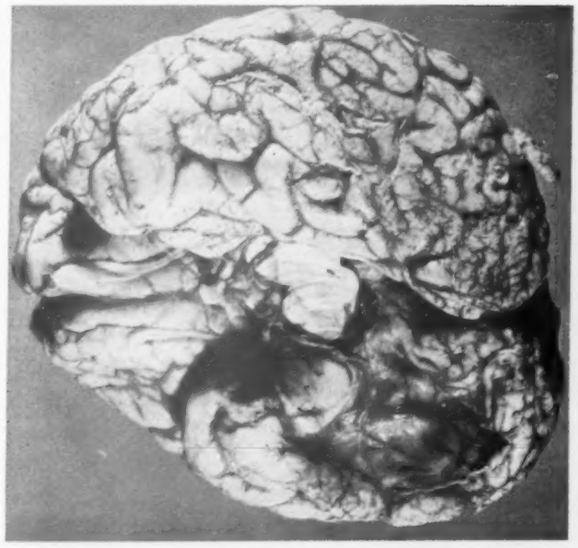


FIG. 2. Brain viewed from below, showing atrophy with asymmetry of cerebral hemispheres due to multiple areas of old infarction. These are scattered throughout the cortex, the larger ones being in the parietal lob[illegible].

The patient was discharged on April 16, 1954, with the diagnoses of "chronic brain syndrome due to intrinsic vascular disease, atrophy of optic nerve and thrombophlebitis of iliac veins."

Anticoagulant therapy was maintained over the next two years but there was little improvement in the mental picture which alternated from euphoria to profound depression. Three weeks before the patient's final admission on May 23, 1956, a productive cough and fever developed. On physical examination she was apathetic, confused and withdrawn. The temperature was 99.8°F. and the pulse 112. An apical systolic murmur was heard and there was dullness over the left lung base. The abdominal viscera were not palpable. Vision in the right eye was markedly limited and the disc was pale. The reflexes were more active on the left than on the right side.

On readmission to the hospital the temperature ranged from 100 to 105°F., the pulse from 100 to 120. On June 5, 1956, the patient was given a transfusion of 1,000 cc. of blood because of hematemesis and melena. She was generally semistuporous, frequently lapsing into coma and sweating profusely. On June 14 and 15, 1956, several grand mal seizures occurred and the patient died one hour after the last convulsive episode.

Laboratory examinations during this hospital period showed a hemoglobin of 10 gm. per cent; white blood cells, 20,000 per cu. mm.; polymorphonuclears, 89 per cent; smears showed elliptocytosis, occasional spherocytes, and poikilocytes. The platelets were observed to be decreased on smear. All bone marrow elements were hyperplastic, including megakaryocytes. The Coombs' test was negative; the erythrocyte sedimentation rate, 35 mm. in the first hour; prothrombin time, twenty-three seconds; serum protein, 6.2 gm. per cent. Serum electrophoresis gave the following values: gamma globulin, 1.6 gm./100; alpha-1, 0.62 gm./100; alpha-2, 0.50 gm./100; beta globulin, 1.8 gm./100; albumin, 1.9 gm./100. The cephalin cholesterol test was 3-plus; thymol turbidity, 5 units; thymol flocculation test, 4-plus; serum non-protein nitrogen, 57 mg./100 cc. Examination of the urine showed albumin, 2-plus, granular casts and red blood cells. Chest roentgenogram revealed densities up to 15 mm. in diameter diffusely scattered throughout both lungs. Carotid arteriogram showed no filling of the right anterior cerebral artery. Electrocardiogram showed auricular fibrillation at a rate of 160. The diagnoses considered were periarteritis nodosa, lupus erythematosus, sarcoidosis and torulosis. Thrombotic thrombocytopenic purpura was suggested during the 1953 hospitalization and was reconsidered during the final illness but dismissed from serious consideration because of the prolonged course and the absence of purpura.

At autopsy marked pallor was noted but there was no purpura or jaundice. Five hundred cubic centimeters of clear fluid was present in each pleural cavity. The heart weighed 240 gm.; a mural thrombus was present in the left auricular appendage. The free margin of the mitral valve and its chordae tendineae were slightly thickened and a verrucous vegetation was attached to the atrial aspect of the posterior cusp. It measured 2 cm. in diameter and was elevated about 1 cm. above the cusp. The superficial portion was friable and the base hard, containing calcium salt deposits. No evidence of bacterial infection was found. There was extensive organizing pneumonia in both lungs. Many emboli were present in large and small pulmonary vessels and there were old and recent areas of infarction, some of which were infected and exuded pus from their cut surfaces. The spleen was enlarged and congested; it weighed 520 gm. The liver

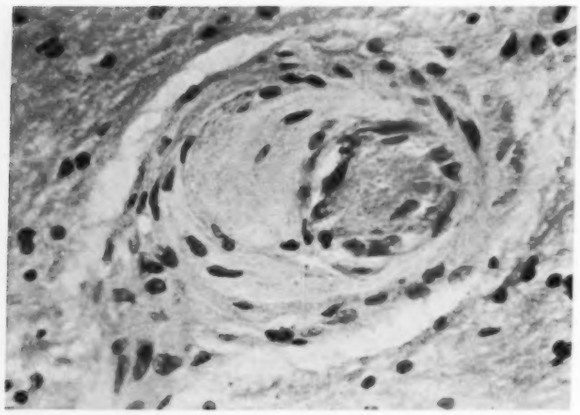


FIG. 3. Capillary in cerebral cortex showing granular eosinophilic material both in lumen and in wall. Hematoxylin and eosin, original magnification × 900.

weighed 1,750 gm. The kidneys were small (120 gm. each) and granular. The brain weighed only 940 gm. (Fig. 2.) There was extensive cortical atrophy with multiple areas of encephalomalacia in both hemispheres. The blood vessels of the circle of Willis and the superficial vessels of the brain showed no gross evidence of arteriosclerosis.

On microscopic examination the capillaries and arterioles and possibly occasional venules from multiple sites (i.e., myocardium, lungs, spleen, liver, kidneys, myometrium, ovarian stroma, posterior pituitary, adrenal cortex, parathyroids, cerebral and cerebellar cortex) showed unusual changes, both intraluminal and intramural. There was a smudgy eosinophilic material in the vessel wall generally beneath an intact endothelium. (Fig. 3.) Within the lumen there was partial or complete occlusion by a more eosinophilic mass. This intraluminal material varied in appearance being smudgy, finely granular, (Fig. 4), or even occasionally containing myceliumlike threads. Marked proliferation of the endothelium

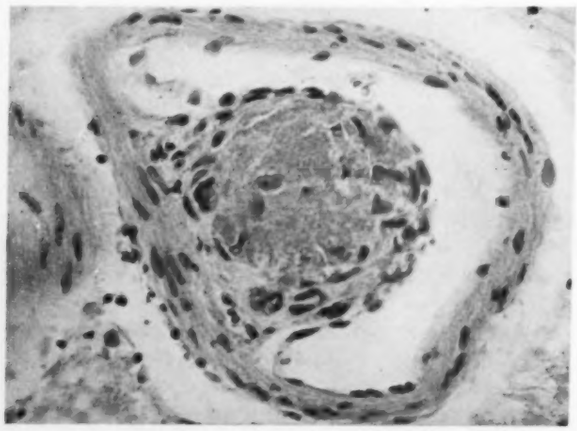


FIG. 5. Polypoid mural lesion covered by endothelium. Hematoxylin and eosin, original magnification × 560.

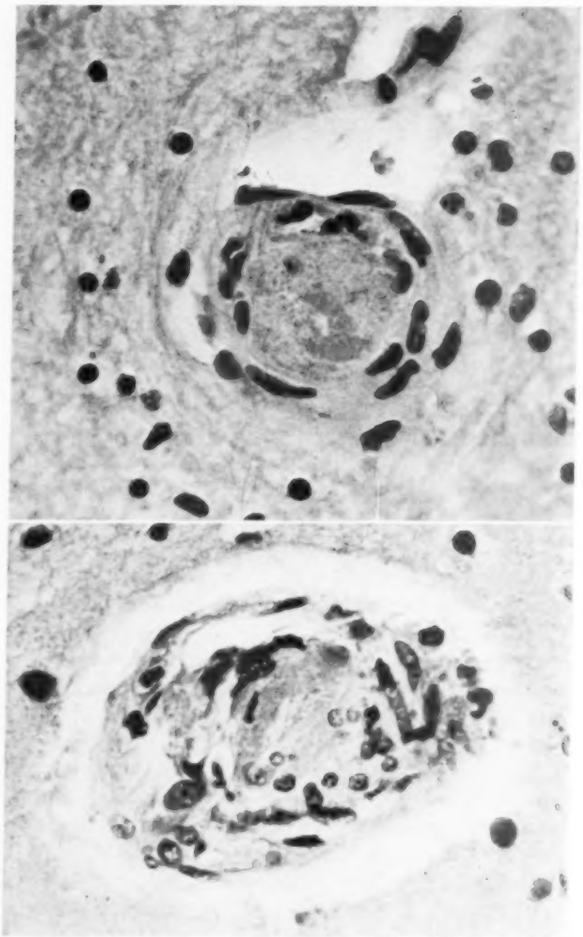


FIG. 4. Two cerebral capillaries demonstrating granular nature of the intraluminal deposit. Top, fresh lesion. Original magnification × 700. Bottom, older lesion with endothelial proliferation. Hematoxylin and eosin, original magnification × 845.

was seen. In some vessels the mural lesion projected in a polypoid fashion into the lumen of the vessel and was covered by large endothelial cells. (Fig. 5.) Rarely, accumulation of the eosinophilic material was found outside the vessel wall in the adventitial tissue. The intravascular material of recent deposition was brightly eosinophilic whereas the older lesions showed varying degrees of organization and recanalization.

Periodic acid-Schiff stains of both the intraluminal and intramural material were positive, and in azure eosin stains no nuclear structures were seen, except where occasional leukocytes were entrapped. The Verhoeff elastic stain showed some disruption and fragmentation of elastic fibers in the regions of eosinophilic accumulations.

Additional histologic findings included minute foci of myocardial necrosis and fibrosis, moderate fatty change in the liver, minute areas of pancreatic necrosis and dilatation of acini, and renal arteriolar

sclerosis with a membranous and proliferative glomerulitis. There was normoblastic hyperplasia of the marrow and numerous megakaryocytes were present.

COMMENTS

In the prolonged clinical courses of many of these cases there have been periods in which the illness has been indistinguishable from the rapidly fulminating cases, the only differences being in the ensuing periods of remission. Generally the terminal events in the patients with prolonged survival mimic exactly the acute, less protracted illness. Of the cardinal clinical features of the disease (fever, thrombocytopenia, anemia and central nervous system involvement) all have been present in the majority of these patients but the failure in any case to manifest one or another feature appears to be of no great significance.

Evidence of disordered serum proteins, particularly of the globulin moiety was found in eight of the cases included in this review. (Table I.) In the absence of disease of the liver abnormality of the thymol turbidity and cephalin flocculation tests may, according to some authors [*24*], be taken as indicating some abnormality of serum proteins. The association of false positive serologic tests for syphilis with hyperglobulinemia has frequently been reported [*25,26*]. It appears that thrombotic thrombocytopenic purpura may be added to the list of specific "hyperglobulinemic diseases" [*24*] and also to the list of diseases exhibiting biologic false positivity for syphilis [*25*]. According to the observations of Feinstein and Petersdorf [*24,25*] abnormality of the cephalin–cholesterol test is more likely to be associated with hypoalbuminemia whereas the thymol turbidity is more apt to be abnormal in the presence of elevated serum globulins.

In four of the present cases sensitivity to drugs is reported in the history. In four cases, including the one reported by the authors, proliferative or exudative glomerular lesions are described. Glomerular changes have also been described in some of the acute cases of thrombotic thrombocytopenic purpura and may be offered together with the disordered serum proteins and other manifestations of hypersensitivity as evidence indicating a possible relationship with the so-called collagen diseases. Emphasis has been laid on the frequent parallelism between some cases of thrombotic thrombocytopenic purpura and cases of disseminated lupus erythematosus. In three patients of the present series there was laboratory or morphologic evidence suggestive of the possible coexistence of the two conditions.

TABLE I
SERUM PROTEIN VALUES*

Case No.	Serum Albumin (gm. %)	Serum Globulin (gm. %)	Serum Beta Globulin (gm. %)	Serum Gamma Globulin (gm. %)	Thymol Turbidity Units	Cephalin Flocculation Test
6	4.0	3.1	...	...	.....	4+
7	4.0	4.0	...	...	.....	.....
8	4.1	2.8	...	...	.....	.....
9	3.4	4.1	...	...	.....	3+
10	...	....	...	...	4	.....
11	4.2	1.9	...	...	.....	.....
12	3.5	3.3	...	...	.....	.....
13	...	....	...	3.4	12.9	4+
14	3.8	1.7	...	...	.....	.....
15	...	2.95	...	...	Normal	Normal
16	3.8	4.6	...	1.6	8.4	1+
19	1.4	1.8	0.3	1.1	8	3+
20	1.9	4.4	1.8	1.6	5	3+

* No information on Cases 1 to 5, 17 and 18.

Six instances of a positive Coombs' test in thrombotic thrombocytopenic purpura have been reported [*8,14,16,27–29*] and three of the patients fall into the group analyzed here. It is interesting that in one of them there was a marked reduction in antibody titer following ACTH therapy and disappearance of antibodies following splenectomy.

Splenectomy has been performed in eighteen patients suffering from thrombotic thrombocytopenic purpura, as reported in the literature. Eight of the patients in the group with a protracted course were subjected to splenectomy. Two were living in complete remission thirty-two months following surgery, one was well twelve months postoperatively, and remissions of two years and of nine months, respectively, occurred in two others. A remission of one month followed splenectomy in a sixth patient, while two patients failed to survive the procedure.

There was clinical evidence of thrombophlebitis in five patients and of gross infarcts of various organs in eight of the patients discussed in this paper. In two of the patients included in this review manifestations of the Raynaud syndrome occurred.

Vegetations of one or both of the atrioventricular valves were found in ten of the patients coming to autopsy in the cases compiled from the literature. Mural thrombi were present in the left atrial appendage in two patients. The lesions were generally of the non-bacterial verrucous vegetative type, although in two patients with

terminal sepsis the lesions were of bacterial nature. Attempts have been made to identify the material forming the vegetations with the intraluminal deposits seen in the small blood vessels.

In only two of the cases of acute thrombotic thrombocytopenic purpura have there been reports of non-bacterial verrucous endocarditis [*11,30*], and in one of them the clinical course was prolonged to six weeks. The pathogenesis of non-bacterial endocardial vegetations has been considered by Allen and Sirota [*31*] to be of valvular origin and not thrombotic in nature. In all cases we were impressed by the similarity in morphologic appearance between the endocardial lesions and the so-called "platelet-thrombi." The possibility remains that the mechanisms that play a part in this disease act also on the substance of the heart valve if the course is sufficiently prolonged to allow for this development.

MacDonald and Robbins [*32*] point out that such endocardial lesions as are here described may be of great significance as sources of emboli and, as seen in the cases reviewed in this paper, infarction of various viscera and thrombosis of large vessels does occur in an appreciable number of those patients who demonstrate the endocardial lesions.

The spleen was enlarged in eleven of the twenty patients of the present group, the weights ranging from 350 to 1,000 gm. This is presumed to be a reflection of the marked hemolytic activity which occurs sporadically in this disease. Central nervous system involvement is stated to occur late in the course of thrombotic thrombocytopenic purpura. Even though this is not invariable the findings in the present series suggest that in the cases of more prolonged survival serious involvement of the central nervous system generally occurs late and is usually directly related to the fatal outcome.

Originally described by Moschcowitz [*2*] as agglutinated red cells and by Baehr et al. [*1*] as platelets, the nature of the occlusive material in thrombotic thrombocytopenic purpura is still undetermined. Using fluorescein-labeled anti-human platelets from a rabbit, no specific reaction could be shown by Craig and Gitlin [*33*] in tissues from patients with this disorder. These authors, and more recently Dixon [*34*] using this technic, suggest that these lesions are composed of fibrin or perhaps fibrinogen. In this regard it is of interest to recall that Seegers and his group [*35*] have described the presence of fibrinogen in the platelets. Johnson et al. [*36*] have studied a patient with normal plasma fibrinogen levels in whom they found significantly lowered platelet fibrinogen.

SUMMARY

The clinical and autopsy findings in a case of thrombotic thrombocytopenic purpura of at least three and probably many more years' duration are reported. The presence of the characteristic vascular lesions was demonstrated in retrospect in surgical material obtained three years before death and a positive serologic test for syphilis, later ascertained to represent a biologic false positive reaction, was discovered eighteen years before death.

The literature on thrombotic thrombocytopenic purpura is reviewed and nineteen cases of prolonged survival are analyzed. It is pointed out that endocardial vegetations and occlusion of large blood vessels occur in cases of prolonged thrombotic thrombocytopenic purpura. The occurrence of disordered serum proteins is emphasized. It is suggested that platelet-derived fibrinogen may form the occlusive material in the arterioles and capillaries.

REFERENCES

1. Baehr, G., Klemperer, P. and Schifrin, A. An acute febrile anemia and thrombocytopenic purpura with diffuse platelet thrombosis of capillaries and arterioles. *Tr. A. Am. Physicians*, 51: 43, 1936.
2. Moschcowitz, E. Acute febrile pleiochromic anemia with hyaline thrombosis of terminal arterioles and capillaries. *Arch. Int. Med.*, 36: 89, 1925.
3. Brown, E. B. and Norman, J. W. Multiple platelet thrombi. *New York J. Med.*, 46: 2167, 1946.
4. Engel, G. L., Scheinker, I. M. and Humphrey, D. C. Acute febrile anemia and thrombocytopenic purpura with vasothromboses. *Ann. Int. Med.*, 26: 919, 1947.
5. Beigelman, P. M. Variants of platelet thrombosis syndrome and their relationship to disseminated lupus. *Arch. Path.*, 51: 213, 1951.
6. Meacham, G. C., Orbison, J. L. and Heinle, R. W. Thrombotic thrombocytopenic purpura; disseminated disease of arterioles. *Blood*, 6: 706, 1951.
7. Symmers, W. St. C. and Barrowcliff, D. F. Platelet thrombosis syndrome. *J. Path. & Bact.*, 63: 552, 1951.
8. Gardner, F. H., McElfresh, A. E., Harris, J. W. and Diamond, L. K. Effect of adrenocorticotrophic hormone (ACTH) in idiopathic acquired hemolytic mechanisms. *J. Lab. & Clin. Med.*, 37: 444, 1951.
9. Gendel, B. R., Young, J. M. and Kraus, A. P. Thrombotic thrombocytopenic purpura. *Am. J. Med.*, 13: 3, 1952.

10. Monroe, W. M. and Strauss, A. F. Intravascular hemolysis; morphologic study of schizocytes in thrombotic purpura and other diseases. *South. M. J.*, 46: 837, 1953.
11. Vassar, P. S. and Spain, D. M. Platelet thrombosis syndrome. *Circulation*, 8: 664, 1953.
12. Popper, H. P. and Kushner, D. S. (Editors). Cardiovascular-Renal Problems. Clinical Pathologic Conferences. Cook County Hospital, Chicago, vol. 1, p. 139. New York, 1954. Blakiston.
13. Fisher, E. R. and Creed, D. L. Thrombotic thrombocytopenic purpura; report of case with discussion of its tinctorial features. *Am. J. Clin. Path.*, 25: 620, 1955.
14. Baez-Villasenor, J. and Ambrosius, K. Thrombotic thrombocytopenic purpura; report of a case with some unusual characteristics. *Ann. Int. Med.*, 46: 378, 1957.
15. Siegel, B. M., Friedman, I. A., Kessler, S. and Schwartz, S. O. Thrombohemolytic thrombocytopenic purpura and lupus erythematosus. *Ann. Int. Med.*, 47: 1022, 1957.
16. Shapiro, H. D., Doktor, D. and Churg, J. Thrombotic thrombocytopenic purpura (Moschcowitz's disease); report of a case with remission after splenectomy and steroid therapy. *Ann. Int. Med.*, 47: 582, 1957.
17. Nussbaum, M. and Dameshek, W. Transient hemolytic and thrombocytopenic episode (? acute transient thrombocytopenic purpura), with probable meningococcemia; report of a case. *New England J. Med.*, 256: 448, 1957.
18. Rodriguez, H. F., Babb, D. F., Perez Santiago, E. and Costas-Durieux, J. Thrombotic thrombocytopenic purpura; remission after splenectomy. *New England J. Med.*, 257: 983, 1957.
19. Scalfi, L., Bruzzese, L. and Piomelli, S. Porpora tromboticatrombocitopenica cronica, intermittente. *Minerva med.*, 48: 2821, 1957.
20. Fitzgerald, P. J., Auerbach, O. and Frame, E. Thrombocytic acroangiothrombosis (platelet thrombosis of capillaries, arterioles and venules). *Blood*, 2: 519, 1947.
21. Gasser, C., Gautier, E., Steck, A., Siebenhann, R. E. and Oechslin, R. Hämolytisch-urämische Syndrome: bilaterale Nierenrindennekrosen bei akuten erworbenen hämolytischen Anämien. *Schweiz. med. Wchnschr.*, 85: 905, 1955.
22. Allison, A. C. Acute haemolytic anaemia with distortion and fragmentation of erythrocytes in children. *Brit. J. Haemat.*, 3: 1, 1957.
23. Shumway, C. N., Jr. and Miller, G. An unusual syndrome of hemolytic anemia, thrombocytopenic purpura and renal disease. *Blood*, 12: 1045, 1957.
24. Feinstein, A. R. and Petersdorf, R. G. Clinical significance of hyperglobulinemia. I. Diagnostic implications. *Ann. Int. Med.*, 44: 899, 1956.
25. Feinstein, A. R. and Petersdorf, R. G. Clinical significance of hyperglobulinemia. II. Correlation with liver function tests, serologic tests for syphilis, and bone marrow examinations. *Ann. Int. Med.*, 44: 925, 1956.
26. Moore, J. E. and Mohr, C. F. Biologically false positive serologic tests for syphilis type, incidence, and cause. *J. A. M. A.*, 150: 467, 1952.
27. Ritz, N. D., Groisser, V. W. and Banowitch, M. M. Thrombotic thrombocytopenic purpura with a positive Coombs reaction. *Am. J. Med.*, 21: 468, 1956.
28. Dacie, J. V. The Haemolytic Anemias; Congenital and Acquired, p. 372. New York, 1954. Grune & Stratton.
29. Wasserman, E. Thrombohemolytic thrombocytopenic purpura. Case report and review of literature. *Am. J. Med.*, 24: 648, 1958.
30. Dickenman, R. C., Brown, H. J., Hiratzka, T. and Vetne, G. Thrombotic thrombocytopenic purpura with associated afibrinogenemia; report of case. *J. Michigan M. Soc.*, 54: 1421, 1955.
31. Allen, A. C. and Sirota, J. H. Morphogenesis and significance of degenerative verrucal endocardiosis (terminal endocarditis, endocarditis simplex, nonbacterial thrombotic endocarditis). *Am. J. Path.*, 20: 1025, 1944.
32. MacDonald, R. A. and Robbins, S. L. Significance of nonbacterial thrombotic endocarditis: an autopsy and clinical study of 78 cases. *Ann. Int. Med.*, 46: 255, 1957.
33. Craig, J. M. and Gitlin, D. The nature of the hyaline thrombi in thrombotic thrombocytopenic purpura. *Am. J. Path.*, 33: 251, 1957.
34. Dixon, F. J. Immunohistochemical analysis of hypersensitivity and related lesions. In: Henry Ford Hospital International Sumposium on the Mechanisms of Hypersensitivity. To be published.
35. Ware, A. G., Fahey, J. L. and Seegers, W. H. Platelet extracts, fibrin formation and interaction of purified prothrombin and thromboplastin. *Am. J. Physiol.*, 154: 140, 1948.
36. Johnson, S. A., Monto, R. W. and Caldwell, M. J. A new approach to the thrombocytopathies; thrombocytopathy A. *J. Appl. Physiol.* (In press.)

Polyneuritis with Albuminocytologic Dissociation in the Spinal Fluid in Systemic Lupus Erythematosus*

Report of a Case, with Review of Pertinent Literature

MARTIN GOLDBERG, M.D. *and* HATAI CHITANONDH, M.D.

Philadelphia, Pennsylvania *Thonburi, Thailand*

AMONG the collagen diseases peripheral neuropathy is well established as part of polyarteritis nodosa. However, relatively few reports have appeared in the literature describing polyneuropathy in systemic lupus erythematosus (S.L.E.). Moreover, to our knowledge only two papers have appeared describing cases of polyneuropathy in S.L.E. emphasizing that the changes in the spinal fluid were compatible with the syndrome of "neuronitis" [*1,2*].

It is the purpose of this paper to present a case of S.L.E. in which a symmetrical polyneuropathy developed in association with spinal fluid changes suggestive of a Guillain-Barré syndrome [*3*] with two exacerbations and partial remissions, and to describe in detail the clinical course and therapy. This will be followed by a review of the literature in an attempt to clarify the above entity as a part of the picture of S.L.E.

CASE REPORT

F. T., a fourteen year old Negro girl, was admitted to the Philadelphia General Hospital on January 18, 1958, with the complaint of inability to move her arms or legs. Except for the usual childhood diseases she had been in good health and asymptomatic until she was ten years of age (1954) when she first noted a rash on her forehead. This rash, which was non-pruritic and non-tender, gradually spread over a period of one year to involve her right cheek and the extensor aspects of both arms, hands and thighs. In the fall of 1955, a biopsy specimen of the skin showed the changes of discoid lupus. During this period, aside from her non-pruritic skin rash, the patient was asymptomatic. She noted no increased sensitivity to sunlight. Various medications at several skin clinics failed to improve the rash.

In March 1957 the patient had a rather abrupt onset of feverishness, fatiguability, exertional dyspnea and pain, heat, swelling, and limitation of motion of both knees. Simultaneously with the above symptoms her skin lesions became secondarily infected. She was admitted to another hospital where an x-ray examination of the chest revealed pericardial effusion. Several L.E. cell preparations were positive. Treatment with prednisone, 60 mg./day, and antibiotics resulted in dramatic symptomatic improvement in forty-eight to seventy-two hours. The patient was discharged in May 1957 clinically improved, and was taking prednisone 5 mg./day and para-aminobenzoic acid (PABA) 20 gm./day.

While taking this medication the patient was asymptomatic until early December 1957 when she began to experience difficulty in raising her arms above her head due to "weakness." This weakness of her arms became progressively worse. Two weeks after onset she began to notice weakness in both lower extremities, finding it difficult to climb stairs. This symptomatology progressed rapidly, and by December 18, 1957, she was unable to move all four extremities voluntarily except the toes. During this period of time, the patient experienced no associated pain, paresthesia or dysesthesia. On December 25, 1957, her temperature "spiked" to 104°F. orally and she was again hospitalized elsewhere for twelve days. Upon discharge her condition had not improved. On January 18, 1958, she was admitted to the Leaman medical service of the Philadelphia General Hospital.

Physical examination revealed a thin, well developed adolescent girl with inability to move all four extremities. The temperature was 99.8°F., the pulse 104, the blood pressure was 92/60 mm. Hg and respiration 26. The skin showed scaling, hyperpigmentation and slight follicular accentuation of the face and scalp with secondary areas of alopecia. There were numerous discrete papules with crusting over the extensor surfaces of her fingers, hands, upper and lower arms, thighs and legs. The skin over all the

* From the Department of Medicine, Philadelphia General Hospital, Philadelphia, Pennsylvania.

fingers was tight, shiny and atrophic with tapering of the tips of the fingers. Funduscopic examination revealed no abnormalities. The neck was supple and there was no venous distension. There were a few crepitant inspiratory rales in her right lung base posteriorly. Examination of the heart revealed a diffuse point of maximum impulse in the sixth left intercostal space in the anterior axillary line. P_2 was split and markedly accentuated. There was a soft grade 2 apical systolic murmur. There was no significant adenopathy. There was no joint tenderness, swelling or deformity. No peripheral edema was present.

On neurological examination the patient was mentally clear, alert, cooperative, emotionally stable with intact memory for recent and remote events. There was profound weakness almost to the point of flaccid paralysis of all four extremities. In the upper limbs both distal and proximal (shoulder girdle) musculature was weak; dorsiflexion or volar flexion of her wrists could not be done nor could she move her fingers. In the lower extremities the patient was only able to wiggle her toes slightly. Dorsiflexion and plantar flexion of the toes could not be done against force. All sensory modalities were intact including touch, pain, vibration and position senses. All tendon reflexes and the abdominal reflexes were absent. There were no pathological reflexes present. The cranial nerves were all intact. The patient was able to use the muscles of her neck and trunk, and function of the sphincters was normal.

Laboratory data revealed a hemoglobin of 10.9 gm./100 cc. The white blood cell count was 2,780/cu. mm. with 52 per cent neutrophils (14 per cent band cells, 38 per cent segmented cells), 32 per cent lymphocytes, 14 per cent monocytes, 1 per cent plasma cells. The reticulocyte count was 0.3 per cent. Blood urea nitrogen was 9 mg. per cent. Fasting blood sugar was 116 mg. per cent. The serum total proteins were 5.9 gm. per cent with an A/G ratio of 2.3/3.6. The serum sodium was 125 mEq./L., and CO_2 combining power 17.1 mEq./L. The calcium was 10.8 mg. per cent. The Kolmer and V.D.R.L. serologic tests for syphilis were non-reactive. Urinalysis showed a specific gravity of 1.008, a rare red blood cell, occasional hyaline cast, and a trace of protein. Lumbar puncture on January 24, 1958, showed a clear spinal fluid with a pressure of 120 mm. of water. The protein was 340 mg. per cent, sugar 70 mg. per cent, chlorides 772 mg. per cent. There were no cells present. Roentgenogram of the chest on January 24, 1958 showed generalized cardiomegaly with straightening of the left border of the heart. The lung fields were clear. An electrocardiogram was read as showing right ventricular hypertrophy. An L.E. cell preparation using clotted peripheral blood was positive for L.E. rosettes and L.E. cells. Electrophoresis of serum proteins showed: total 6.9 gm. per cent, albumin 1.98 gm. per cent, alpha-1 globulin 0.40 gm. per cent, alpha-2 globulin 0.76 gm. per cent, gamma globulin 3.13 gm. per cent. The electromyographic studies on January 24, 1958 were made selecting the left anterior tibial and the left biceps brachii muscles. The patterns showed that fibrillation potentials were present with the patient at rest. Voluntary contraction elicited a reduced number of motor unit potentials. These were of low amplitude (100 microvolts); some were of normal configuration but some were polyphasic. Conduction velocity of the right ulnar nerve was 30 meters/second and the ratio of maximum area/threshold area was 11.3. These were compatible with renervation of the muscles, since "nascent" motor unit potentials are often of low amplitude, polyphasic and are present with fibrillation potential. The slow conduction velocity is consistent with peripheral neuropathy and "neuronitis."

The patient was treated with prednisone 20 mg./day for one week, followed by gradual tapering of dosage to 5 mg./day by February 4, 1958. Concomitant with the steroids, a comprehensive program of physical therapy was begun. By January 22, 1958 (four days after admission), the patient had improved to the point where she was able to sit with support and partially feed herself. She then showed a gradual but progressive improvement in her motor function, and by the end of February 1958 she had regained almost full use of motor power in her upper extremities and partial recovery of motor power in her legs. Although she could voluntarily move all muscle groups in her lower extremities, there was still weakness and she was unable to stand without firm support. During this period the patient had a persistent low grade temperature varying between 99.6°F. and 101.0°F. as well as a sinus tachycardia while at rest ranging from 110 to 130. A staphylococcal urinary tract infection responded to therapy with novobiocin and chloramphenicol, and her skin lesions were stationary. The patient subjectively felt quite well and was cheerful.

However, on March 26, 1958 (the sixty-eighth hospital day), a temperature of 102.6°F. developed rather abruptly associated with severe "aching" pains in her calf muscles, thigh muscles and the muscles of her back. On March 27 her temperature rose to 104.0°F. and examination revealed marked tenderness in her calf and thigh muscles and total loss of cutaneous pain and light touch as well as vibration sensation in both lower extremities from her toes to her knees. She had a pulse of 140; P_2 was "booming" in quality and her liver edge was palpable 2 cm. below the right costal margin. Because of impending congestive failure she was digitalized. By March 31 the patient had total flaccid paralysis of all four extremities as well as the muscles of the back of her neck. The muscles of respiration and those innervated by the cranial nerves were unaffected. Funduscopic examination was within normal limits. Pain, temperature, touch, vibration and position sensations

TABLE 1
STUDIES OF SPINAL FLUID DURING HOSPITALIZATION

Data	Dates				
	1/24/58	3/27/58	4/3/58	4/14/58	5/16/58
Pressure (mm. H_2O).....	120	300	200	55	260
Protein (mg. %).....	340	144	360	..	340
Cells (white blood cells/ cu. mm.)...	0	12	0	..	0
Colloidal gold	...	3455432100	3455543210	..	...

were totally absent in the distal parts of all four extremities. On March 27 administration of prednisone was increased to 30 mg./day and on March 30 to 60 mg./day. The patient became afebrile with a pulse of 96 on March 28, and by April 1 her muscle pain and tenderness had almost completely disappeared. This was associated with marked increase in motor function in the upper extremities. By April 3 she had only weakness in flexion and extension of her fingers, but the lower extremities were showing only moderate improvement. She could not wiggle her toes and could display motion weakly in the quadriceps, ileopsoas and tibialis anticus muscles bilaterally. By April 9 a good deal of her sensory functions had returned except for hypalgesia and absent vibration sense in both lower extremities. She was now also able to move her fingers well and make a weak fist. Prednisone therapy, 60 mg./day, was continued for twenty-one days after which the dosage was tapered by 5 mg. increments every fourth day to 30 mg./day and then by 2.5 mg. increments every fourth day.

Lumbar puncture at the onset of the above exacerbation (on March 27) revealed a clear fluid with a pressure of 300 mm. of water. The spinal fluid protein was 144 mg. per cent and there were 12 white blood cells and 6 red blood cells/cu. mm.; the sugar was 30 mg. per cent, the chlorides were 656 mg. per cent; the colloidal gold curve was 3455432100. A gram stain showed no organisms; a smear for acid-fast bacilli was also negative. The hemoglobin was 9.0 gm. per cent, peripheral white blood cell count was 8,100/cu. mm. with one metamyelocyte, 92 per cent neutrophils (44 per cent segmental forms and 47 per cent band forms), 1 per cent lymphocytes and 7 per cent monocytes. The serum electrolytes were normal. Two blood cultures were negative. A chest roentgenogram on April 16 showed marked decrease in the cardiac size as compared to previous x-ray films, with straightening of the left border of the heart indicative of a resolving pericardial effusion.

While taking steroid therapy plus physical therapy the patient has continued to make progressive improvement. By May 14, she was able to sit up and feed herself. She was able to stand supporting herself on parallel bars. Motor power had returned to all muscle groups, although she was unable to walk due to residual weakness of her quadriceps femori and tibialis antici. She was still totally areflexic. Sensory examination revealed areas of hypalgesia up to her mid-tibia on the left and up to her ankle on the right in a "stocking" type of distribution. Vibration sense was still absent in the lower extremities up to her hips but was present elsewhere. She has remained afebrile and has never shown any changes in sensorium or manifestations of central nervous system involvement. At present (May 20, 1958), the patient is walking with support and is ready for discharge.

COMMENTS

This fourteen year old girl had the onset of her disease at age ten with the development of a rash. Her subsequent clinical course which included the development of a disseminated skin rash, fever, arthritis, pericarditis, as well as leukopenia, hyperglobulinemia, positive biopsy specimens of the skin and several positive L.E. cell preparations leave little doubt as to the diagnosis of systemic lupus erythematosus.

Her two exacerbations of polyneuropathy were interesting in regard to some of their differences. The first episode was totally motor in type as characterized by a marked degree of paralysis in all four extremities with absent reflexes. She had neither subjective nor objective evidences of sensory impairment. Her second episode was of the mixed type with affection of both motor and sensory systems. The latter included loss of cutaneous pain and temperature, touch, vibration and position sensations in a "glove and stocking" distribution in all four extremities. She also had severe pain and tenderness in her calf and thigh muscles. It is interesting that the vibration sense has been one of the last modalities to return. Cases of both a motor and a sensorimotor type have been described in the Guillain-Barré syndrome [*3*].

Studies of the patient's spinal fluid showed a persistent elevation of protein with few or no cells. (Table 1.) She also had an elevated spinal fluid pressure throughout most of the course. Neither the degree of elevation of the protein nor the pressure paralleled closely the course of the disease.

In support of the concept that the neuropathy was an integral part of her lupus syndrome rather than the chance coincidental occurrence of a separate disease is the fact that during the second exacerbation the patient's other symptoms of

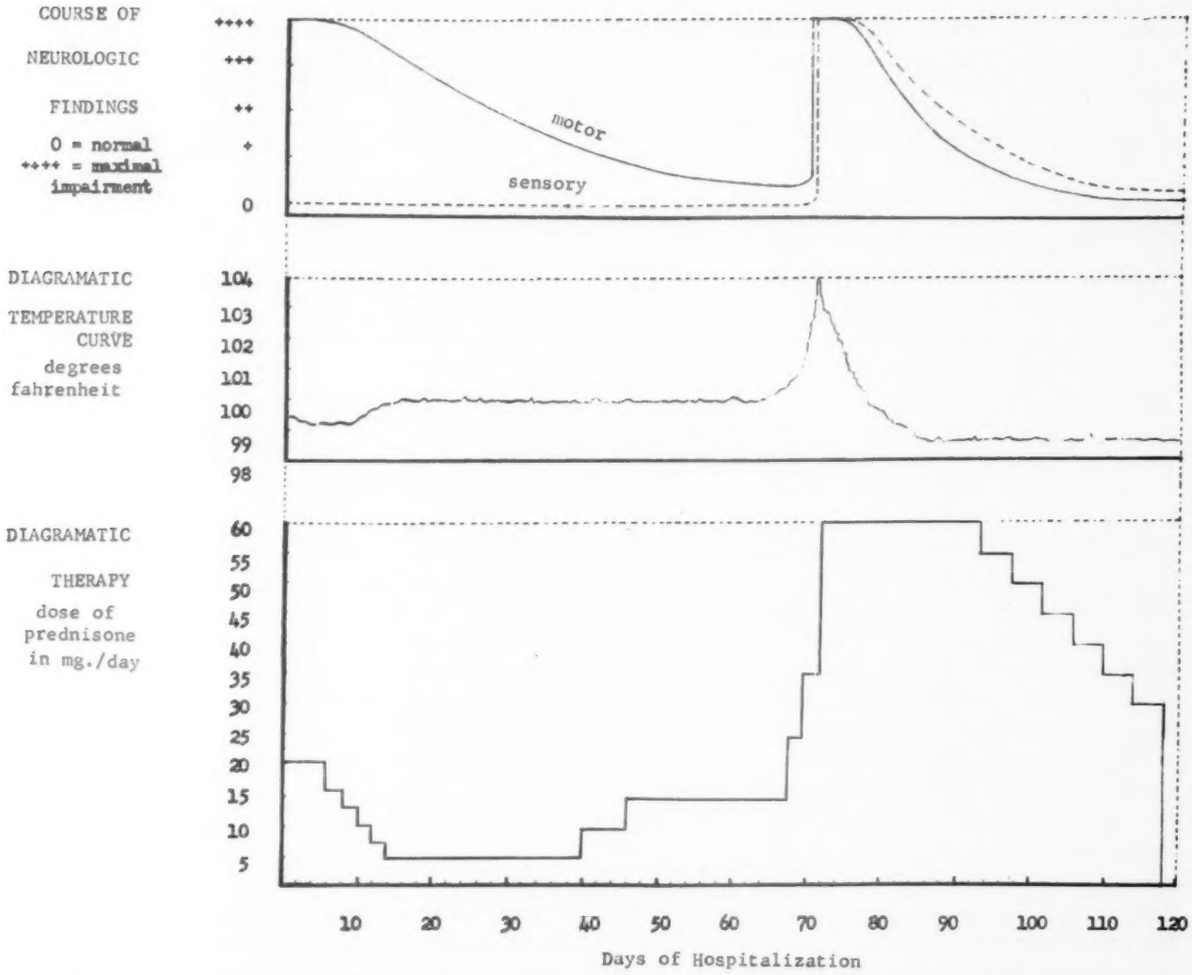


FIG. 1. Diagram of course of neurologic findings in relation to therapy and patient's temperature curve.

lupus were also manifest such as high fever, marked tachycardia and congestive failure.

The patient's response to steroid therapy is worthy of comment. (Fig. 1.) On both occasions, the neurological manifestations improved with increased dosage of prednisone. During the first episode, the maximum dosage was 20 mg./day, and although her neuropathy improved, she continued to show low grade "lupus activity" as manifested by low grade fever and persistent tachycardia. However, with 60 mg./day of prednisone therapy during the second episode, the patient became afebrile and her pulse rate decreased markedly.

Although involvement of the central nervous system has been described many times in S.L.E. [*4*], relatively few investigators have documented polyneuropathy as part of S.L.E., and still fewer have mentioned the Guillain-Barré syndrome in association with S.L.E. Table II summarizes the cases in the literature of symmetrical polyneuropathy with albuminocytologic dissociation in the spinal fluid in S.L.E.

In 1940, Ginzler and Fox [*5*] mentioned the incidental finding of peripheral mononeuritis in a few patients at autopsy. Sedgwick and Von Hagen [*2*] in 1948 described a case which they diagnosed as neuronitis in which the patient exhibited generalized weakness and numbness of the hands with a "glove" hypesthesia in the upper extremities, patchy hypesthesia in the lower extremities, slight weakness of the hand grip, a Babinski sign on the left side and an increased spinal fluid protein content. However, there was little to support the diagnosis of S.L.E. except for the biopsy of a facial skin rash.

Heptinstall and Sowry [*6*] in 1952 were the first to describe a case of peripheral neuritis in

TABLE II

SUMMARY OF FINDINGS OF THE CASES IN THE LITERATURE OF SYMMETRICAL POLYNEUROPATHY AND ALBUMINOCYTOLOGIC DISSOCIATION IN SYSTEMIC LUPUS ERYTHEMATOSUS

Authors	Date	Motor Findings	Sensory Findings	Spinal Fuid	Diagnosis of Systemic Lupus Erythematosus	Autopsy
Sedgwick and Von Hagen [2]	1948	Generalized weakness; weakness of hand grip	Glove hypesthesia in upper extremities; patchy hypesthesia in lower extremities	Pressure, normal; protein, 240 mg. %; cells, 3 lymphocytes/cu. mm.	Biopsy specimen of skin	None
Heptinstall and Sowry [6]	1952	Weakness in upper extremities; paralysis in lower extremities; all deep tendon reflexes absent	Slight loss of 2-point discrimination, touch in hands; light touch and vibration impaired in lower limbs in "stocking" distributions; marked tenderness in calf	Pressure, 170 mm. H_2O; protein, 120 mg. %; cells, 5 lymphocytes/cu. mm.	Autopsy only	Yes
Bailey, Sayre and Clark [1]	1956	Case I: Moderate to marked weakness in all limbs (proximally more than distally at first, and later the opposite); all deep tendon reflexes absent	At first, impaired position sense in fingers and toes; then impaired vibration, stereognosis and light touch in hands and feet	Protein, 240 mg. %; "otherwise normal"	L.E. preparation of sternal marrow; autopsy	Yes
		Case II: Generalized weakness of limbs (proximally more than distally); all deep tendon reflexes absent; partial remission, then exacerbation	Reduced 2-point discrimination and stereognosis in hands; partial remission, then exacerbation with paresthesias, absent vibration and hyperalgesia in lower leg and feet	Protein, 150 mg. %; cells, 3 lymphocytes/cu. mm.; colloidal gold, 1343210000	L.E. preparation of sternal marrow; autopsy	Yes
Scheinberg [10]	1956	First, moderate to minimal weakness in all limbs and decreased Achilles reflexes; then progression to severe weakness in all limbs (distally more than proximally); absent deep tendon reflexes; then partial remission–able to work	First, absent vibration and position at ankles, then generalized with "glove-stocking" hypesthesia; then partial remission with normal results in sensory examination prior to death	Pressure (mm. H_2O), 500, 200–280, 180–160; protein (mg. %), 270, 460–528, 345–535; cells/cu. mm., 7, 0, 0	L.E. preparation of peripheral blood; autopsy	Yes

S.L.E. verified by autopsy. Their patient displayed symmetrical motor involvement with weakness in all four extremities, absent reflexes and definite sensory impairment with absence of light touch and vibration in a "stocking" distribution in the lower extremities. Of significance is the presence of an elevated spinal fluid protein and pressure with only 5 lymphocytes/cu. mm. Although not mentioned by the author, this picture is compatible with a Guillain-Barré syndrome. Dubois [7] and Jessar et al. [8] merely mentioned having observed polyneuritis and neuronitis, respectively, in association with S.L.E.

Clark and Bailey [9] (1954) in describing the neurologic and psychiatric findings in 100 consecutive cases of S.L.E. mentioned an incidence of polyneuropathy in 3 per cent. In 1956, two significant reports of polyneuropathy in S.L.E. with autopsy findings appeared in the literature. Bailey, Sayre and Clark [1] reported five cases of proved S.L.E. with neuritis, in two of which necropsy was performed. Cases III, IV and V were instances of minimal peripheral nerve involvement of mononeuritis "multiplex" rather than a symmetrical polyneuropathy. The latter is the type usually seen in polyarteritis nodosa. However, Cases I and II were examples of true symmetrical polyneuropathy, and in these patients the spinal fluid proteins were definitely elevated with no cells in one case and 3 lymphocytes/cu. mm. in the other. Case I was a thirteen year old girl who displayed moderate to marked weakness of the muscles of the extremities, more marked proximally than distally, absent deep tendon reflexes and marked decrease in position sense of the fingers and toes. Cortisone therapy resulted in "improvement" over two months after which the patient became febrile, and examination revealed impairment of position, vibration, stereognotic sensations in the hands and feet; muscular atrophy and weakness was more pronounced distally. The patient also now had evidence of involvement of the central nervous system. This time the patient did not respond to a "course of cortisone." Case II was a twenty-one year old girl who had "tingling" of the finger tips, toes, feet and tongue, absent tendon reflexes, muscular weakness (proximally

more than distally) with impaired 2-point discrimination and stereognosis of the hands. She had a remission for about a year and then an exacerbation with weakness and paresthesias, and subsequently absent vibration sensation and hyperalgesia in her legs and feet developed. She received cortisone but subsequently died with thrombocytopenia and seizures. It is interesting to note that similar to our patient, both of the patients just mentioned had remissions and exacerbations of their neurologic disorders, with response to steroid therapy in one instance. The authors commented that the clinical picture plus findings in the spinal fluid of the patient just mentioned were consistent with the syndrome of "neuronitis (Guillain-Barré)."

Scheinberg [*10*] described in detail the course, therapy and findings at autopsy in an eighteen year old girl with proved S.L.E. and symmetrical polyneuritis but also with involvement of the central nervous system. Her polyneuropathy started with generalized weakness in all extremities, decreased reflexes in the Achilles tendons and absent vibration and position sensation at the ankles. In one month there developed generalized decrease in vibration and position senses and "glove and stocking" hypesthesia despite treatment with cortisone. Several studies of the spinal fluid showed elevated pressures and protein content, with no cells. Severe weakness in all extremities developed in the patient with only traces of motion distally and fair to good motion proximally and absent tendon reflexes. Over a two-month period the patient's condition improved gradually while taking cortisone therapy and she was able to walk, but she eventually died due to cardiopulmonary failure. Here again the symmetrical polyneuropathy is associated with an albuminocytologic dissociation in the spinal fluid. However, the patient had involvement of the central nervous system concomitant with the aforementioned, and the latter could also account for the protein and pressure changes.

Thus our case makes the fifth detailed description in the literature of proved S.L.E. in association with a symmetrical polyneuropathy of the Guillain-Barré type. Although most cases of Guillain-Barré syndrome are of unknown etiology, this picture has been seen in association with infectious mononucleosis [*3*], and similar clinical and spinal fluid findings may on occasion be seen [*11*] in alcoholism, vitamin deficiency, heavy metal poisoning, diphtheritic and diabetic neuropathy, porphyria, postparalytic poliomyelitis and tumors of the spinal cord and brain. In none of these conditions is the L.E. cell test positive and clinical differentiation from S.L.E. usually offers no difficulties.

The pathologic changes observed at autopsy in S.L.E. with polyneuropathy are interesting and help to give some insight into the pathogenesis of the disorder. Heptinstall and Sowry [*6*], on examination of the peripheral nerves in the legs, noted evidence of damage to numerous arterioles in the epineurium, i.e., previous obliteration of arteriolar lumens with recanalization and surrounding inflammatory cells while other arterioles showed eccentric fibrotic thickening in the intimal zone with thinning of the overlying muscular wall. They concluded that the peripheral neuritis in their case was due to ischemia secondary to lesions of vessels supplying the nerves. Dubois [*7*] states that he has seen a case of polyneuritis due to involvement of the nutrient vessels but gives no details. In Case I of Bailey, Sayre and Clark [*1*], microscopy of the nervous system also showed an arteriolitis of the vessels supplying the peripheral nerves with arteriolar wall necrosis and polymorphonuclear cellular infiltration in and about the arteriolar walls. They also described diffuse degeneration of the axis cylinders, and many of the spinal ganglion neurons showed degenerative changes in association with almost complete degeneration of the posterior columns of the spinal cord. In Case II, however, evidence for vasculitis in the epineurium was minimal, but again there was degeneration of the posterior spinal ganglia and complete loss of myelin in the posterior columns. Microscopy of peripheral nerves in Scheinberg's [*10*] case revealed separation of individual nerve fibers and displacement of the epineurium from the nerve bundles by grayish blue amorphous material. This material stained faintly blue with hematoxylin and was considered to be related to hematoxylin bodies observed in the blood vessels. The author postulated that the polyneuritis was due to compression of the nerve fibers by the deposition of this amorphous material. Thus it can be seen that there is more than one possible mechanism for the development of polyneuropathy in S.L.E. There may be degenerative changes in the peripheral nerves secondary to vasculitis, and, independently, there can be primary degenerative changes of the peripheral nerves, spinal ganglia, and posterior columns. Both of these types of pathologic

changes can produce the clinical picture of a symmetrical polyneuropathy which, in the cases of S.L.E. reported on so far, is associated with an increased spinal fluid protein, few or no cells, and in some instances (our case included) an elevation in spinal fluid pressure.

SUMMARY

A case of systemic lupus erythematosus with symmetrical polyneuropathy and albuminocytologic dissociation in the spinal fluid is presented in detail describing the clinical course and therapy. The patient had two exacerbations with only motor involvement in the first episode and both motor and sensory impairment in the second episode. Review of the literature reveals four other cases of polyneuropathy in S.L.E. with similar findings in the spinal fluid. The pathogenesis of the neuropathy may be either a vasculitis of the nutrient vessels of the peripheral nerves or a primary degeneration of the nerves, posterior root ganglia or posterior columns of the spinal cord.

ADDENDUM

The patient was discharged on July 15, 1958, and her condition was stable until October 15, 1958, when she was hospitalized for two weeks for a basilar pneumonitis that responded to therapy. Upon discharge some increased weakness in her quadriceps and tibialis anticus muscles was noted. On December 10, 1958, she was readmitted to the hospital because of several subcutaneous skin abscesses and a relapse in her neurological condition manifested by: (1) increased generalized weakness; (2) ataxia and Romberg's sign; (3) absent vibration and markedly impaired position sense in both lower extremities; (4) hypesthesia below both knees and distal to both elbows; (5) diminished vibration sense in the upper extremities below her elbows; and (6) spinal fluid pressure of 220 mm. of water and a protein of 200 mg. per cent. Thus her third exacerbation of polyneuropathy manifested predominantly posterior column signs. Increasing the dosage of prednisone from 20 to 40 mg. daily caused about 75 per cent improvement in her neurological condition. She was discharged on March 3, 1959, but was readmitted on March 16, 1959, with the picture of a fulminant bronchopneumonia and left-sided pleuritis. She died on March 19, 1959. An autopsy was performed by Dr. Morton Robinson and the organs and sections were reviewed by Dr. William E. Ehrich. Dr. Helena Riggs examined the central and peripheral nervous system.

Positive findings on the general examination were: (1) healed skin lesions of chronic discoid lupus; (2) 600 cc. of serofibrinous fluid in the left pleural cavity and 400 cc. of clear pericardial fluid; (3) right ventricular hypertrophy (the right ventricle was 0.7 cm. in average thickness); (4) shaggy, fibrinous adhesions almost completely covering the left lung which had several areas of atelectasis and both lungs showed multiple pale indurated areas which on microscopic examination proved to be areas of bronchopneumonia; and (5) microscopic vascular changes which included: (a) fibrinoid degeneration of the wall of a small coronary artery with a thrombus in the lumen, (b) intimal thickening and fibrosis of scattered pulmonary arterioles, and (c) intimal fibrosis in one arteriole in the kidneys with partial obliteration of the lumen. The vascular lesions were considered to be inactive with the possible exception of the coronary vessel.

The central nervous system showed no gross abnormal changes. Microscopic examination of the nervous system revealed (Fig. 2): (1) greatest damage in the peripheral nerves (sciatic, brachial plexus) with severe loss of myelin, little cellular reaction, a paucity of interstitial collagen and a reduced number of Schwann cells; in the epineurium there were occasional perivascular collections of lymphocytes with an occasional arteriole showing proliferative endarteritis, either crescentic in shape or entirely surrounding the lumen; (2) spotty loss of myelin with more evident interstitial proliferation in the subarachnoid root bundles most severe in the cauda equina and lower cervical region with preservation of the cell bodies of the posterior root ganglia but almost complete myelin loss and only slight reaction; (3) moderate ascending degeneration in the column of Goll in the spinal cord; (4) overall preservation of anterior horn cells; (5) crescentic endarteritis in a single vessel in the cauda; and (6) no focal brain lesions or evidence of fibrinoid degeneration in vessels of the brain.

Thus this patient died due to a severe bronchopneumonia. The vascular changes are compatible with the diagnosis of systemic lupus erythematosus. The lesions of the peripheral nerves, nerve roots and posterior columns (a minimal vasculitis with predominantly degenerative and demyelinizing changes) are compa-

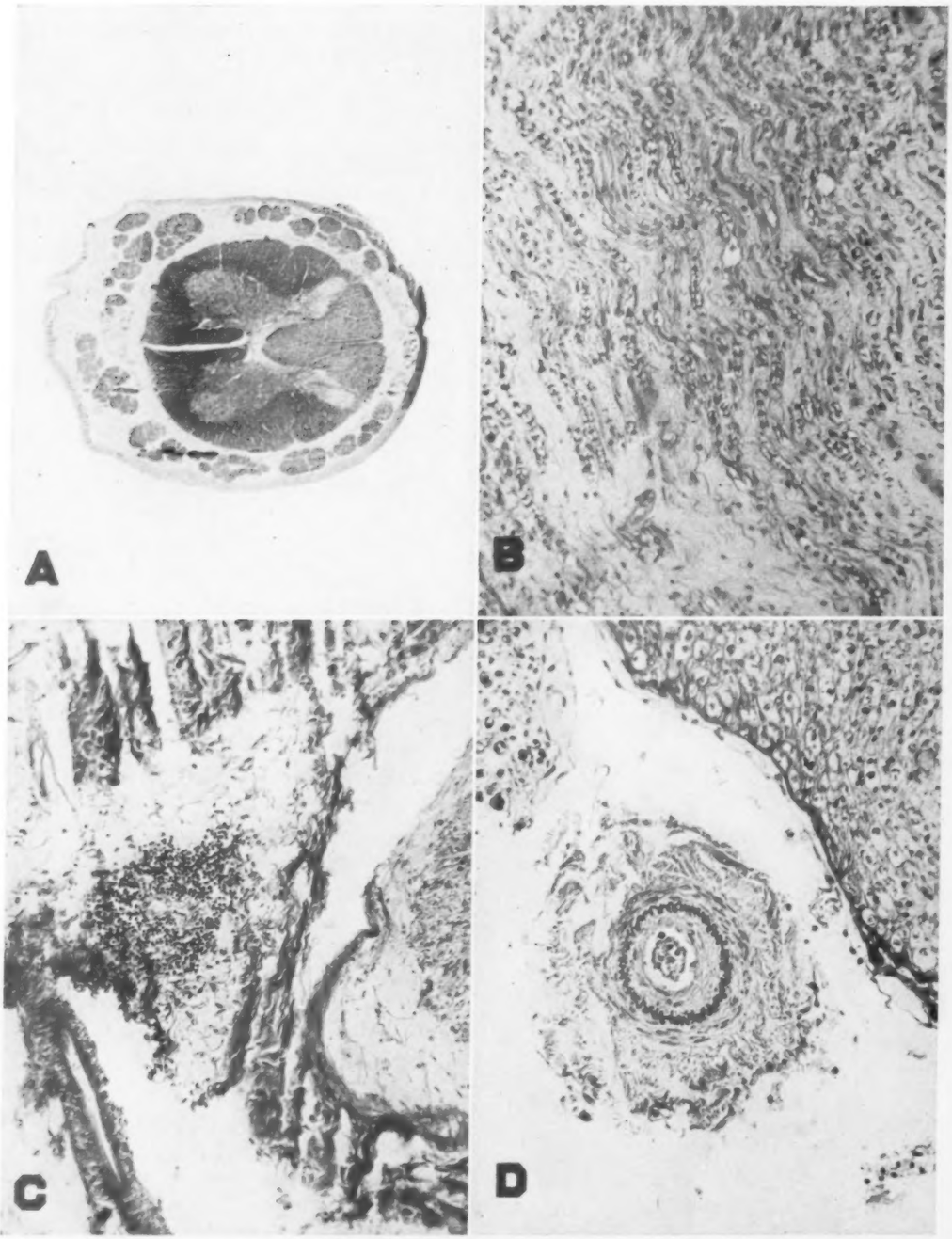


FIG. 2. A, myelin sheath stain. Mild demyelinization in posterior columns of spinal cord with relatively little involvement of subarachnoid root bundles. Original magnification × 15. B, peripheral nerve (sciatic) showing extensive demyelinization with relatively little reaction of Schwann cells and collagen fibers. Hematoxylin and eosin stain, original magnification × 145. C, perivascular lymphocytic infiltration in vicinity of peripheral nerve and adjacent muscle fibers. Hematoxylin and eosin stain, original magnification × 145. D, proliferative endarteritis between root bundles in cauda equina. Hematoxylin and eosin stain, original magnification × 145.

rable to the changes described in the previously reported cases of polyneuropathy in systemic lupus erythematosus.

REFERENCES

1. Bailey, A. A., Sayre, G. P. and Clark, E. G. Neuritis in lupus erythematosus. *Arch. Neurol. & Psychiat.*, 75: 25, 1956.
2. Sedgwick, R. P. and Von Hagen, K. O. Neurologic manifestation of lupus erythematosus and periarteritis nodosa: report of 10 cases. *Bull. Los Angeles Neurol. Soc.*, 13: 129, 1948.
3. Haymaker, W. and Kernohan, S. W. The Landry-Guillain-Barré syndrome. *Medicine*, 28: 59, 1949.
4. Harvey, A. M., Schulman, L. E., Tumulty, P. A., Conley, C. L. and Schoenrich, E. H. Systemic lupus erythematosus: review of literature and analysis of 138 cases. *Medicine*, 33: 291, 1954.
5. Ginzler, A. M. and Fox, T. T. Disseminated lupus erythematosus: cutaneous manifestations of systemic disease (Libman-Sacks): report of cases. *Arch. Int. Med.*, 65: 26, 1940.
6. Heptinstall, R. H. and Sowry, G. S. C. Peripheral neuritis in systemic lupus erythematosus. *Brit. M. J.*, 1: 525, 1952.
7. Dubois, E. L. The effect of L.E. cell test in the clinical picture of systemic lupus erythematosus. *Ann. Int. Med.*, 38: 1265, 1953.
8. Jessar, R. A., Lamont-Havers, W. and Ragan, C. Natural history of lupus erythematosus disseminata. *Ann. Int. Med.*, 38: 717, 1953.
9. Clark, E. C. and Bailey, A. S. Neurologic and psychiatric findings in lupus erythematosus. *Tr. Am. Neurol. A.*, 79: 15, 1954.
10. Scheinberg, L. Polyneuritis in systemic lupus erythematosus: review of the literature and report of a case. *New England J. Med.*, 255: 416, 1956.
11. DeJong, R. N. The Neurologic Examination, 1st ed., p. 742. New York, 1950. Hoeber-Harper Inc.

Diagnosis of Whipple's Disease by Peripheral Lymph Node Biopsy*

Report of a Case

W. Crockett Chears, Jr., M.D., Albert G. Smith, M.D. *and* Julian M. Ruffin, M.D.

Durham, North Carolina

Foamy mononuclear cells are found in the intestine and lymph nodes of patients with Whipple's disease. The cytoplasm of these cells contains a material thought to be a mucopolysaccharide, which is stained by the periodic acid-Schiff (PAS) staining technic [*1*]. These cells crowd the lamina propria of the small intestine. They are also seen in the mesenteric lymph nodes and in other mesenchymal sites [*2*]. When PAS-positive macrophages are found in this distribution they are diagnostic of Whipple's disease. The lipogranulomatosis and lymphangiectasis which are also found in Whipple's disease may be seen in a number of other, apparently unrelated disorders [*3,4*].

The occurrence of characteristic lesions of Whipple's disease in extra-abdominal lymph nodes was first reported by Korsch in 1938 [*5*]. Upton has since reported a widespread mesenchymal distribution of the foam cells in one patient, noting them in hepatic portal triads, in perinephric fat and in vegetations which were found on the heart valves in his patient [*2*]. Puite and Tesluk have emphasized recently that characteristic PAS-positive foam cells may be present in peripheral lymph nodes and have suggested the feasibility of confirmation of a clinical diagnosis by biopsy specimen of a peripheral lymph node [*6*]. Thus the patient may be spared laparotomy which accomplishes nothing other than substantiation of the diagnosis. The purpose of this communication is to report a case in which the diagnosis of Whipple's disease was established antemortem by peripheral lymph node biopsy.

CASE REPORT

The patient, a fifty-three year old white man (Unit No. E-55417), was admitted to Duke Hospital on May 14, 1957, with a complaint of "falling off" and of "loss of energy." For twenty years he had had vague, nondescript abdominal distress and for eight years episodes of stiffness, pain on motion and slight swelling of the wrists. In 1953 he had an exacerbation of his epigastric distress with nausea, vomiting and a rapid loss of weight from 147 to 116 pounds. Abdominal exploration in another hospital disclosed only distention of the duodenum proximal to the superior mesenteric artery, and duodenojejunostomy was performed.

Following operation there was some improvement and a weight gain of 14 pounds, but he never fully recovered. In January, 1957, he became worse and colicky lower abdominal pain developed followed

Table 1
LABORATORY FINDINGS

Data	Findings
Hemoglobin	13 gm./100 ml.
Hematocrit	40%
Leukocytes	11,100
Neutrophils	86%
Eosinophils	2%
Lymphocytes	10%
Monocytes	2%
Sedimentation rate (Wintrobe)	15 mm.
Stool guaiac test	Negative
Stool fat (Sudan III stain)	Increased
Sodium, serum	132 mEq./L.
Potassium, serum	4.5 mEq./L.
CO_2-combining power, serum	25 mEq./L.
Nitrogen, non-protein, serum	43 mg./100 ml.
Calcium, serum	8.2 mg./100 ml.
Phosphorus, inorganic, serum	3.4 mg./100 ml.
Proteins, total, serum	5.1 gm./100 ml.
Albumin	2.6 gm./100 ml.
Globulins	2.5 gm./100 ml.
Cholesterol, total, serum	129 mg./100 ml.
Carotene, plasma	14 μg./100 ml.

* From the Department of Medicine, Duke University Medical Center, and the Department of Pathology, Veterans Administration Hospital, Durham, North Carolina.

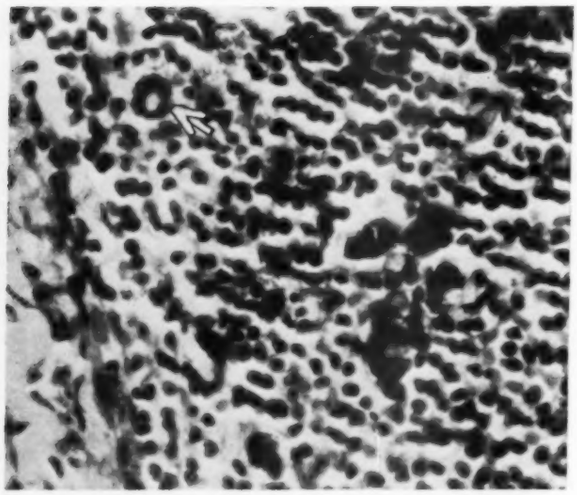


FIG. 1. Axillary lymph node showing a loose aggregation of foam cells with deeply stained, granular cytoplasm (arrow indicates a typical cell). Periodic acid-Schiff stain.

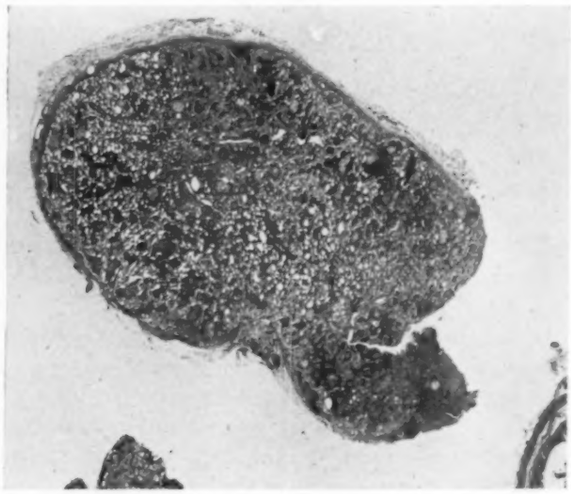


FIG. 2. Mesenteric lymph node showing extensive alteration of structure with large spaces which were presumably fat-filled before fixation. Hematoxylin and eosin.

by a watery diarrhea which was largely nocturnal and was suggestive but not typical of steatorrhea.

He was hospitalized elsewhere and explored for the second time. At operation a dilated upper small intestine and enlarged mesenteric lymph nodes were noted. A lymph node was removed, and appendectomy was performed. He was then referred to Duke Hospital for further study.

At the time of admission he was having mild, vaguely localized, colicky abdominal pain which was relieved by defecation. He stated that his appetite was "not bad." He denied a change of skin color, a bleeding tendency, chills, fever, night sweats, nocturia, syncope or pleurisy. For about three years he had been taking mineral oil two or three times weekly for constipation, which had been present all of his life. There was no family history of arthritis, of a wasting disease or of diarrhea.

Physical examination disclosed an emaciated man who appeared chronically ill. The body weight was 97 pounds, temperature 36.6°C., pulse rate 116, respiratory rate 22, and blood pressure 90/55 mm. Hg. There were petechiae of the skin of the forearms. Noteworthy findings included discrete axillary and cervical lymph nodes, an increased thoracic anteroposterior diameter and a systolic heart murmur. The abdomen showed nothing of significance, and proctoscopy revealed no abnormalities.

The pertinent laboratory findings are shown in Table 1. The electrocardiogram showed non-specific

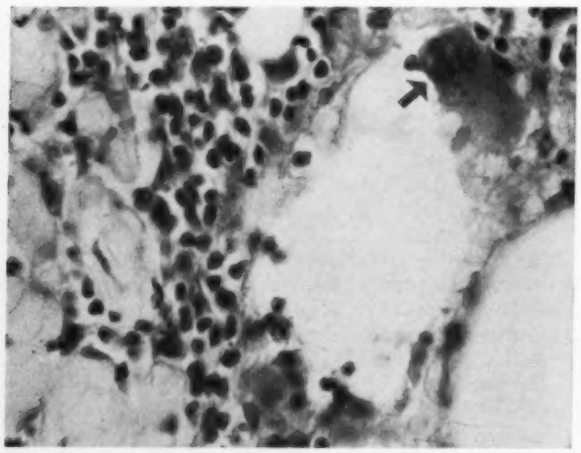


FIG. 3. Mesenteric lymph node under higher magnification showing one of the smaller spaces with an associated multinucleated giant cell (arrow). Hematoxylin and eosin.

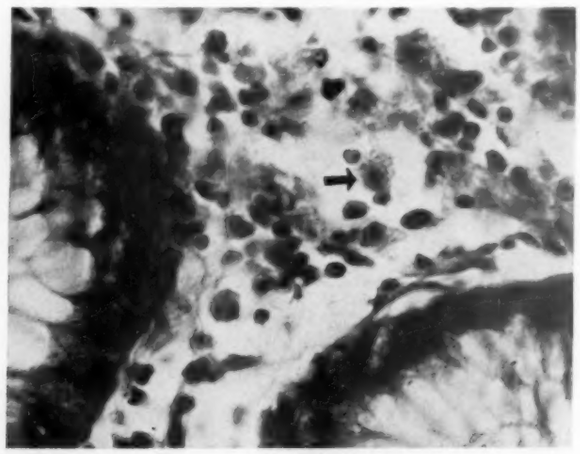


FIG. 4. Appendix showing foam cells (arrow) in the lamina propria. Hematoxylin and eosin.

ST segment and T wave changes consistent with potassium depletion. Roentgenograms showed some pleural thickening in the apices, pulmonary emphysema, and decreased bone density. Ileal study showed the duodenojejunostomy to be functioning properly. There was dilatation and segmentation with thickened mucosal folds throughout the small intestine. The I^{131}-labeled triolein absorption test blood curve was flat (four hours, 1.4; five hours, 1.0; six hours, 1.4 per cent AD/TBV*), and the forty-eight-hour fecal value was 43 per cent AD [7]. The I^{131}-labeled oleic acid absorption test curve was also flat (four hours, 1.1; five hours, 1.7; six hours, 1.8 per cent AD/TBV), and the forty-eight-hour fecal value was 18.5 per cent AD [8]. The glucose tolerance curve was flat.

Based upon these findings a clinical diagnosis of Whipple's disease was made. An axillary lymph node was removed, and sections stained by periodic acid-Schiff (PAS) technic showed an accumulation of PAS-positive mononuclear foam cells singly and in loose aggregates in the sinusoids and lymphoid areas. Some masses of amorphous acidophilic material were also present within this node. (Fig. 1.)

Hematoxylin and eosin stained sections of the mesenteric lymph node and of the appendix removed at another hospital were examined. Material upon which a PAS stain could be made was not available. The section of the mesenteric lymph node revealed hyperplasia of the reticuloendothelial cells of the sinuses, accumulation of what was presumed to be lipid, an adjacent foreign body giant cell reaction, and the formation of epithelioid tubercles containing mononuclear foam cells. (Figs. 2 and 3.) The appendix section revealed the presence of mononuclear cells with foamy cytoplasm in the lamina propria of the mucosa, some of the foam cells appearing in loose aggregates. (Fig. 4.)

The patient was given a gluten-free diet with supplemental vitamins and intravenous corticotropin. He was afebrile throughout his hospital stay. His diarrhea, which was mild, improved somewhat, but he gained no weight and responded poorly to therapy. He was discharged with instructions to continue the same diet and therapy with cortisone, and was not seen again. Apparently he did not respond to treatment and continued to lose weight, weighing only 83 pounds on June 17. He died at home in September 1957. Postmortem examination was not performed.

* AD = administered dose; TBV = total blood volume.

COMMENTS

Whipple's disease should be suspected clinically in any patient having arthralgia, abdominal pain, diarrhea, marked weight loss, lymphadenopathy, and laboratory evidence of impaired intestinal absorption. In the past it has been customary to resort to laparotomy to confirm the diagnosis by histologic examination of a mesenteric lymph node. Such an operation would become unnecessary if the presence of Whipple's disease could be established by biopsy of a peripheral lymph node. The first case to be so diagnosed was reported by Puite and Tesluk [6]. While it is probable that peripheral nodes will not show characteristic lesions in all cases, still it would seem advisable in patients suspected of having Whipple's disease to obtain a biopsy specimen of a peripheral lymph node before subjecting the patient to abdominal surgery.

Acknowledgment: We wish to thank Dr. D. J. Greiner, of The McLeod Infirmary, Florence, South Carolina, for providing tissue sections of the mesenteric lymph node and appendix, and for permission to reproduce them.

REFERENCES

1. Black-Schaffer, B. The tinctorial demonstration of glycoprotein in Whipple's disease. *Proc. Soc. Exper. Biol. & Med.*, 72: 225, 1949.
2. Upton, A. C. Histochemical investigation of the mesenchymal lesions in Whipple's disease. *Am. J. Clin. Path.*, 22: 755, 1952.
3. Hendrix, J. P., Black-Schaffer, B., Withers, R. W. and Handler, P. Whipple's intestinal lipodystrophy. *Arch. Int. Med.*, 85: 95, 1950.
4. Warner, N. E. and Friedman, N. B. Lipogranulomatous pseudosarcoid. *Ann. Int. Med.*, 45: 662, 1956.
5. Cited by Puite, R. H. and Tesluk, H. [6].
6. Puite, R. H. and Tesluk, H. Whipple's disease. *Am. J. Med.*, 19: 383, 1955.
7. Baylin, G. J., Sanders, A. P., Isley, J. K., Shingleton, W. W., Hymans, J. C., Johnston, D. H. and Ruffin, J. M. I^{131}-blood levels correlated with gastric emptying determined radiographically. II. Fat test meal. *Proc. Soc. Exper. Biol. & Med.*, 89: 54, 1955.
8. Isley, J. K., Sanders, A. P., Baylin, G. J., Sharpe, K. W., Hymans, J. C., Ruffin, J. M., Shingleton, W. W. and Wilson, J. R. Use of I^{131}-labeled oleic acid in the study of gastrointestinal function. *Proc. Soc. Exper. Biol. & Med.*, 94: 807, 1957.

Crystalline Glomerular Deposits in Multiple Myeloma*

G. William Sickel, M.D.

Chester, Pennsylvania

Aberrations in protein metabolism, with crystalline deposits in widespread locations, have been described in "reticuloendothelioses," and in multiple myeloma particularly. To our knowledge, review of some twenty-four cases has failed to disclose a case in which such deposits have been demonstrated in the glomeruli of the kidney.

Löhlein [*1*] in 1921 reported a case in which protein crystals were demonstrated in kidney tubules. The author cited this case as the first in which such a demonstration was made. Microscopic examination of kidney sections revealed masses of crystals in dilated tubules of the cortex, and crystal-like exudates in the medullary tubules. The glomeruli were not affected.

In a case of hemorrhagic purpura, huge cells containing a crystalline-like material were interpreted by Agress and Smith [*2*] as being cells of the reticuloendothelial system. Crystalline deposits were demonstrated in the tubules of the kidney, with an accompanying inflammatory reaction; however, the glomeruli were not involved in these crystalline deposits.

Brass [*3*], in a comprehensive study of twelve cases of "plasmacytoma," found generalized crystalline deposits in various organs of the body, but made no mention of glomerular involvement. This same author in 1943 [*4*] reported a case of myeloma in which Bence Jones protein was demonstrated in the urine. The patient died in uremia, and microscopy of the kidney sections showed protein crystals which were recognized as Bence Jones protein precipitates. Again no glomerular involvement was noted. Severe kidney changes were reported by Mücke [*5*] in 1943. Six cases were reviewed, and in two myeloma was responsible for the alteration in protein metabolism. Two other patients were syphilitics, one had "leukemic lymphadenosis" and achylia gastrica; in the sixth case no definite cause could be found. In three of the cases there were crystals within the kidney tubules; in two, tubules and interstitial tissue were involved; and in one case the crystals were intracellular in the epithelium of the tubules. Histologic examination showed an intact glomerular apparatus in these cases.

Other patients with protein crystalline deposits in the renal tubules have been described by Neumann [*6*] and by Sikl [*7*] in 1949. The former also reported crystals in Bowman's capsule. No glomerular involvement was noted. Multiple myeloma with the Fanconi syndrome and rod-shaped inclusions within the tubular epithelium has been reported by Engle and Wallis [*8*]. The glomeruli in this case were normal, except for a few which were sclerotic.

CASE REPORT

A sixty-five year old Negro man (No. C-375) entered the Chester Hospital on January 14, 1956, complaining of cough and chest pain of one week's duration. Two weeks prior to admission he had had a chest cold which had become steadily worse.

The patient denied having kidney disease, rheumatic disease, diabetes, tuberculosis or malignancy. There was no history of weight loss, dysuria or oliguria.

Examination revealed an elderly Negro whose skin was moist and warm. Respiration was not labored. The blood pressure was 170/108 mm. Hg; pulse, 102; respirations, 24 per minute. There was some limitation of chest expansion on the left side. A localized enlargement, 3 to 4 cm. in diameter, was noted over the tenth rib posteriorly. Breath sounds were decreased over the left base, and vocal fremitus was increased. Dullness was present on percussion over the left base. The heart rhythm was regular, at a rate of 102 per minute. There were no murmurs.

* From the Department of Pathology, Chester Hospital, Chester, Pennsylvania.

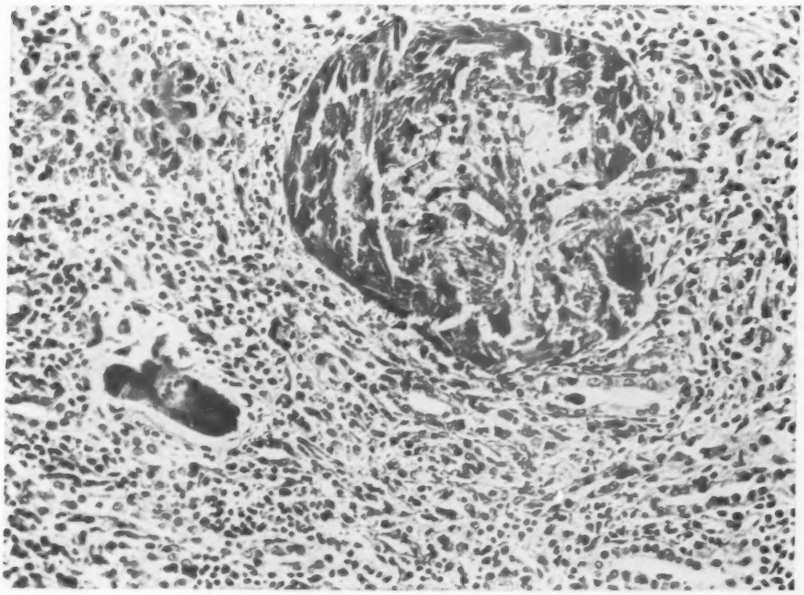


FIG. 1. Photomicrograph showing glomerulus and surrounding tissue, and demonstrating Bence Jones protein crystals in the glomerulus.

Moderate cardiomegaly was noted on auscultation. The diagnosis on admission was pneumonitis, left base.

Roentgenograms of the chest and abdomen taken on admission revealed an enlarged heart, and a possible lesion in the upper left abdominal quadrant. The urine gave an acid reaction, with a specific gravity of 1.009. A trace of proteinuria was noted. Many polymorphonuclear leukocytes, and 1 to 3 red blood cells per high power field were found. The hemoglobin was 8 gm. per cent with a hematocrit of 27 per cent. The leukocytes numbered 6,500 per cu. mm. with 22 per cent band cells, 44 per cent segmented forms, and 29 per cent lymphocytes. Eosinophils numbered 1 per cent and there were 4 per cent metamyelocytes.

The blood urea nitrogen was reported on the second hospital day as 170 mg. per cent; serum calcium, 11.9 mg. per cent; plasma carbon dioxide, 10.2 mEq. per L.; chlorides, 104 mEq. per L.; potassium, 7.7 mEq. per L. and sodium, 148 mEq. per L.

The hospital course was marked by severe oliguria (400 ml. per twenty-four hours), and on January 16 twitching appeared on the left side. The patient was "toxic" and drowsy. The blood pressure was 180/100 mm. Hg. The urine became bloody. The patient began to bleed from the nostrils. On January 17 a repeat electrolyte pattern showed a sodium of 132 mEq. per L., potassium, over 8 mEq. per L; chlorides, 98.2 mEq. per L. The plasma carbon dioxide had fallen to 8.4 mEq. per L. and the urea nitrogen was now 193 mg. per cent. In spite of fluid therapy and other supportive measures coma deepened. Convulsive seizures began, and the patient soon died.

At autopsy (performed by Dr. Walter Levy) the body was that of a fairly well nourished Negro man. Examination of the cardiovascular system revealed a heart weighing 350 gm. There was slight hypertrophy of the left ventricular wall, and the coronaries showed slight sclerosis. The valves, papillary muscles and chordae tendinae were essentially normal. The lungs were bluish gray, soft and doughy in consistency but extremely moist. Some emphysema was noted. No true consolidation was present. The liver presented a picture of chronic passive congestion. The pancreas, gallbladder and gastrointestinal tract were within normal limits, as were the spleen and adrenals.

The grossly similar kidneys were enlarged and bulging, weighing 396 gm. each. Their external surfaces were finely granular, whitish gray with small focal areas of reddish tan color. Section of the kidneys revealed cortical zones which were enlarged to 1.3 cm. in thickness. They were mottled gray, and firm and tough in consistency. The entire cut surface of both organs presented innumerable white, pinpoint-sized dots, and were grossly suggestive of abscesses.

Histologic examination of the kidneys revealed many parts of the nephrons to contain crystalloids of what appeared to be Bence Jones protein. Some crystalloids were needle-shaped, others were rhomboid. They were arranged singly, and in large aggregates. The distal tubules were involved, as were some of the proximal tubules. Many of the glomeruli showed dense crystalline deposits, which in some instances had all but obliterated the glomerular architecture. (Fig. 1.) Other glomeruli contained a minimal number of these crystals. These deposits had evoked a multinucleated foreign body reaction. Many multinucleated giant cells were noted, and around the

glomeruli were many polymorphonuclear leukocytes, lymphocytes and plasma cells. Where the deposits were lighter there appeared to be an early inflammatory infiltrate, without giant cells. The interstitium showed an increased fibrous tissue component. A benign arteriolar nephrosclerosis was present.

Microscopic examination of the spleen revealed a dense plasmacytic infiltration. The lymph nodes showed extramedullary hematopoiesis. A bone marrow examination was not made.

COMMENTS

The diagnosis of multiple myeloma in this patient was unsuspected until the autopsy was performed. This diagnosis was suggested by Dr. Arthur C. Allen [*9*], to whom the kidney sections were sent for study and an opinion. Following receipt of his suggestion an antemortem blood serum sample was studied by electrophoresis through the courtesy of Dr. Robert Norris, the University of Pennsylvania. The results of this study follow:

Albumin	2.5 gm. %	(normal 3.5–4.7)
Alpha$_1$ globulin	0.77 gm. %	(normal 0.16–0.44 gm. %)
Alpha$_2$ globulin	1.33 gm. %	(normal 0.32–0.76 gm. %)
Beta globulin	0.95 gm. %	(normal 0.45–0.93 gm. %)
Gamma globulin	5.76 gm. %	(normal 0.97–1.73 gm. %)
Total protein (biuret)	11.3 gm. %	

This electrophoretic curve certainly would have suggested multiple myeloma had it been available before death.

SUMMARY

A case of multiple myeloma, unsuspected before autopsy, with crystalline deposits in the renal glomeruli is reported. It is postulated that these glomerular deposits were the chief cause of the renal failure, with oliguria, uremia and ultimate death. A brief review of the literature did not disclose previous mention of such crystalline deposits in the glomerular apparatus.

REFERENCES

1. Löhlein, M. Eiweisskrystalle in den Harnkanälchen bei multiplem Myelom. *Beitr. z. Path. Anat. v. z. Allg. Path.*, 69: 295, 1921.
2. Agress, H. and Smith, M. G. Purpura hemorrhagica associated with widespread deposits of crystalline material; reticuloendotheliosis. *Arch. Path.*, 29: 553, 1940.
3. Brass, K. Die Eiweisstoffwechselstörungen des Plasmacytomkranken. *Frankfurt. Ztschr. Path.*, 57: 367, 1943.
4. Brass, K. Die Eiweisstoffwechselstörungen des Plasmacytomkranken. (II. Mitteilung.) *Frankfurt. Ztschr. Path.*, 58: 56, 1943.
5. Mücke, P. Über Ablagerungen von Eiweisskrystallen in der Niere. *Frankfurt. Ztschr. Path.*, 58: 116, 1943.
6. Neumann, V. Multiple plasma cell myeloma with crystalline deposits in the tumor cells and in the kidneys. *J. Path. & Bact.*, 61: 165, 1949.
7. Sikl, H. A case of diffuse plasmacytosis with deposition of protein crystals in the kidneys. *J. Path. & Bact.*, 61: 149, 1949.
8. Engle, R. L. and Wallis, L. A. Multiple myeloma and the adult Fanconi syndrome. *Am. J. Med.*, 22: 5, 1957.
9. Allen, A. C. Personal communication.

Many different

emotional disturbances need

only *one* tranquilizer

Dartal® *t.i.d.*

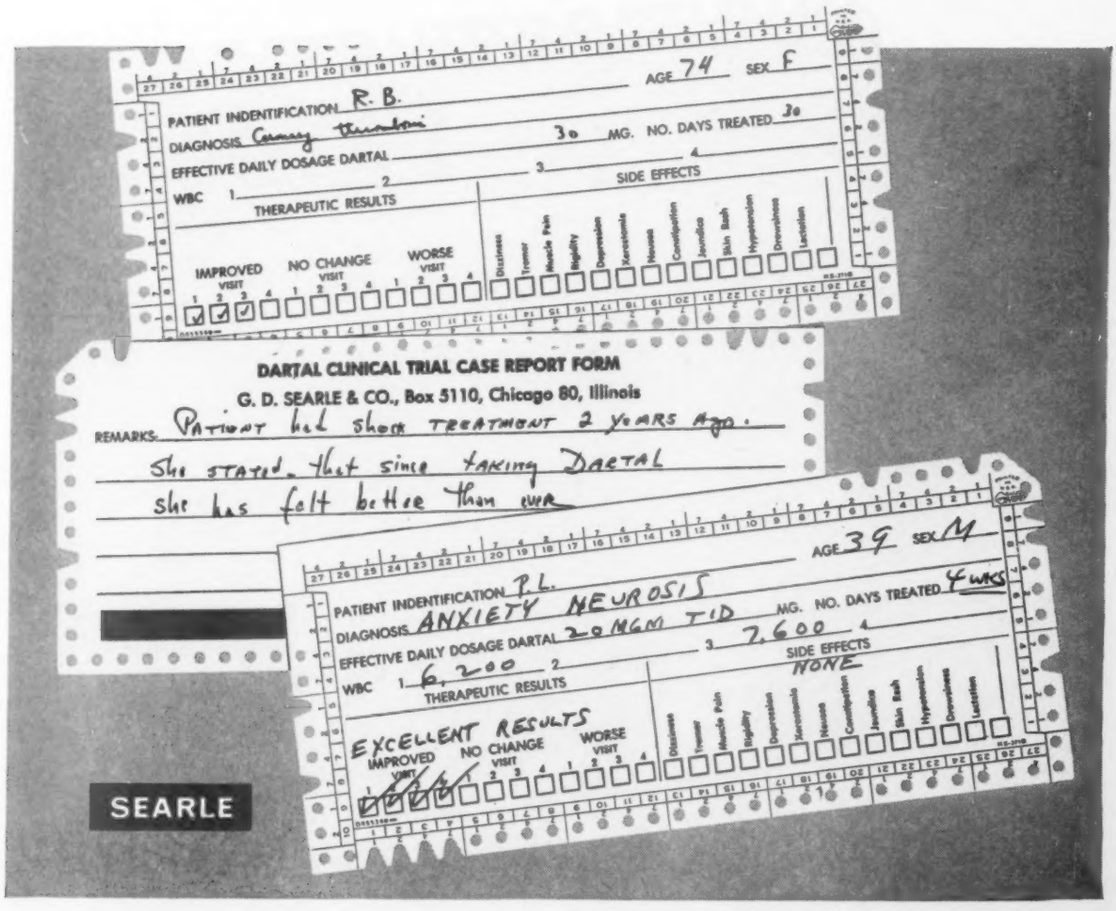
(thiopropazate dihydrochloride)

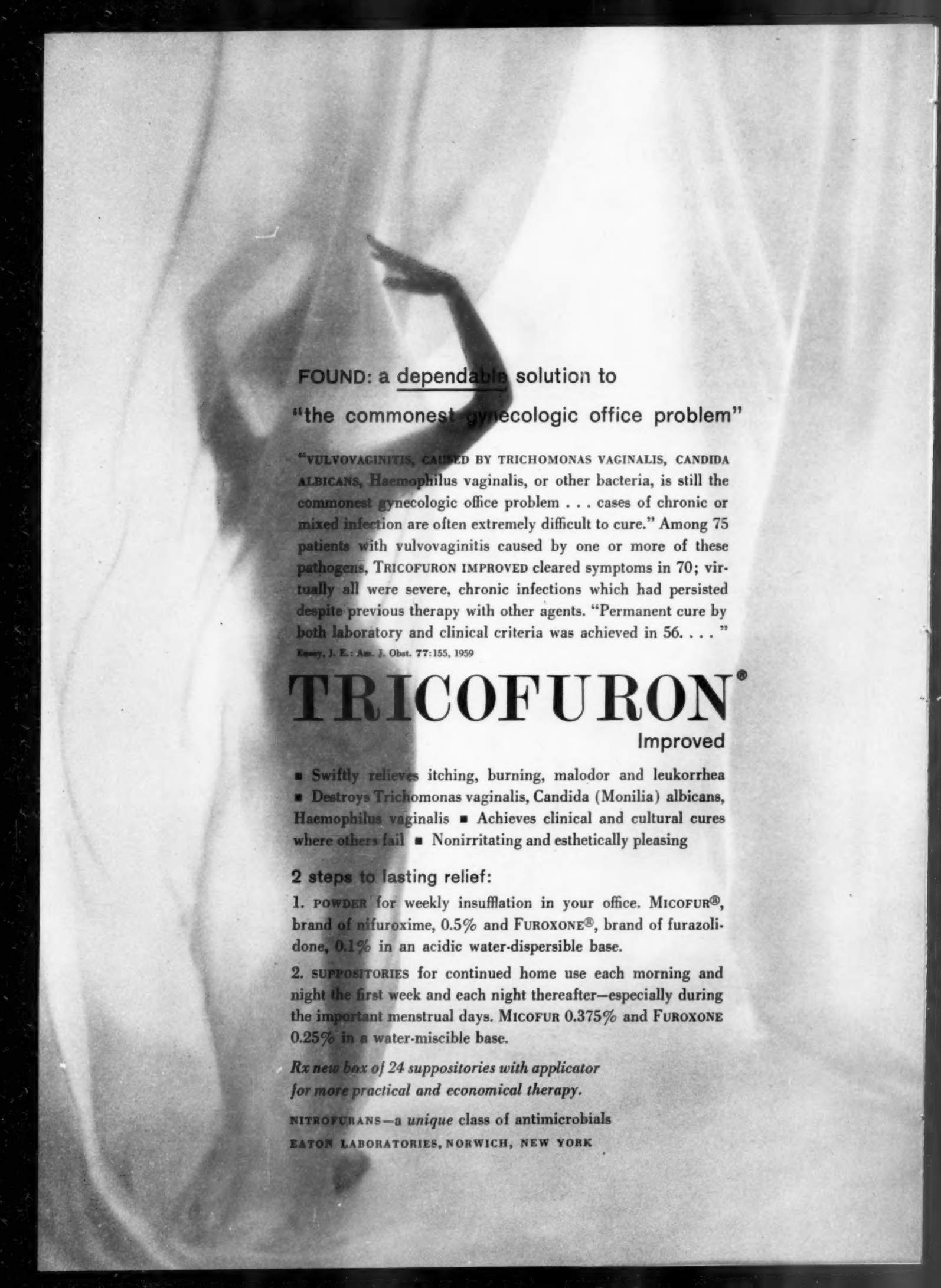
Because of its unusually numerous therapeutic indications and broad range of therapeutic activity, DARTAL is an outstanding tranquilizer for general use.

Dartal produced consistent results not only under controlled clinical conditions but also under conditions of everyday office practice.

	Diagnosis	Number of Patients	Number Improved
Reports from office trials by 156 physicians	Anxiety and Tension States	476	321
	Duodenal Ulcer	14	11
	Irritable Colon (including spastic constipation)	13	8
	Menopausal Syndrome	40	28
	Hypertensive Cardiovascular Disease	14	13

with low dosage: Only one tablet of 2 or 5 or 10 mg. t.i.d.
with relative safety: Evidence indicates that Dartal is not icterogenic.





FOUND: a dependable solution to "the commonest gynecologic office problem"

"VULVOVAGINITIS, CAUSED BY TRICHOMONAS VAGINALIS, CANDIDA ALBICANS, Haemophilus vaginalis, or other bacteria, is still the commonest gynecologic office problem . . . cases of chronic or mixed infection are often extremely difficult to cure." Among 75 patients with vulvovaginitis caused by one or more of these pathogens, TRICOFURON IMPROVED cleared symptoms in 70; virtually all were severe, chronic infections which had persisted despite previous therapy with other agents. "Permanent cure by both laboratory and clinical criteria was achieved in 56. . . . "

Kneey, J. E.: Am. J. Obst. 77:155, 1959

TRICOFURON®

Improved

- Swiftly relieves itching, burning, malodor and leukorrhea
- Destroys Trichomonas vaginalis, Candida (Monilia) albicans, Haemophilus vaginalis
- Achieves clinical and cultural cures where others fail
- Nonirritating and esthetically pleasing

2 steps to lasting relief:

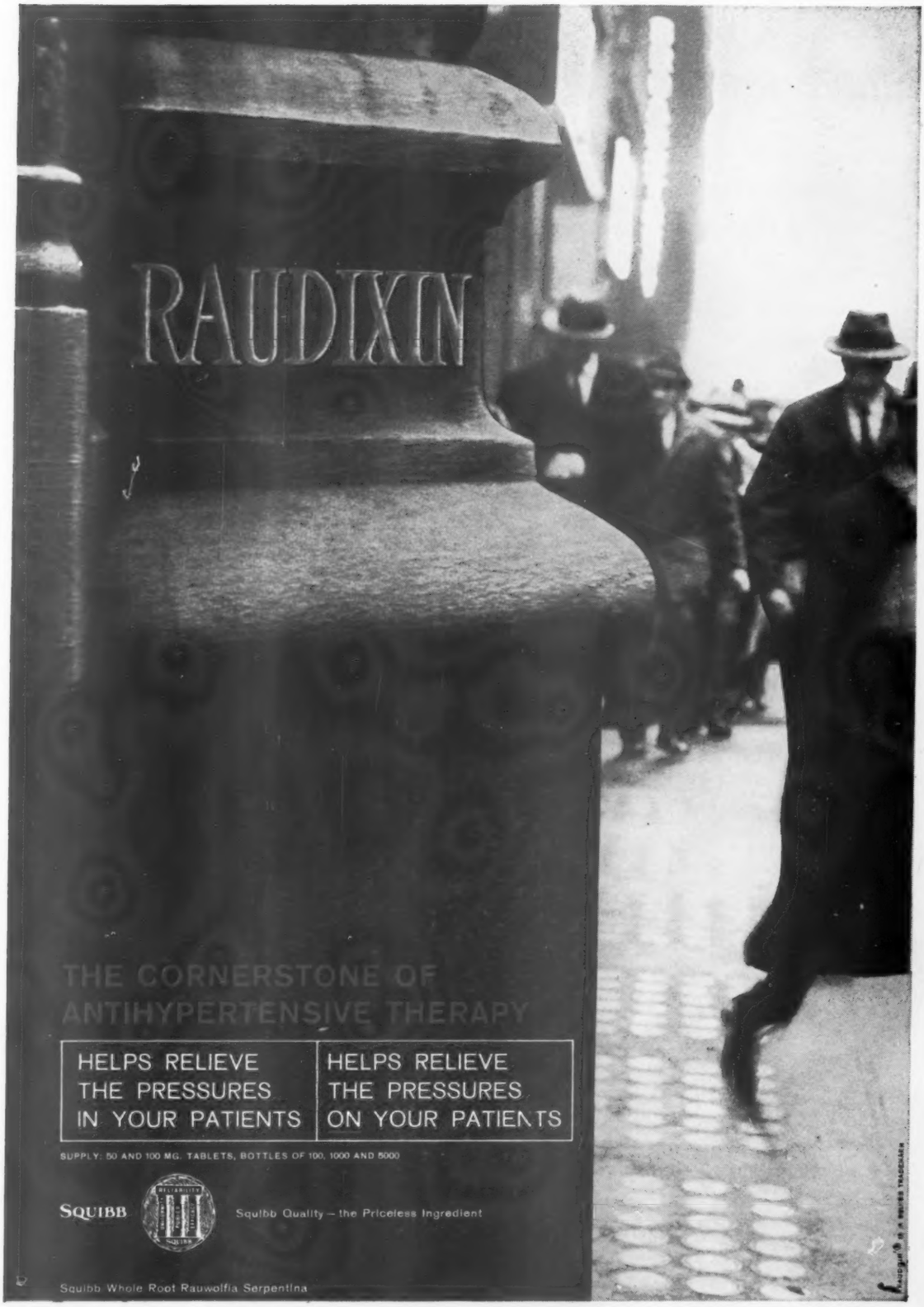
1. POWDER for weekly insufflation in your office. MICOFUR®, brand of nifuroxime, 0.5% and FUROXONE®, brand of furazolidone, 0.1% in an acidic water-dispersible base.

2. SUPPOSITORIES for continued home use each morning and night the first week and each night thereafter—especially during the important menstrual days. MICOFUR 0.375% and FUROXONE 0.25% in a water-miscible base.

Rx new box of 24 suppositories with applicator for more practical and economical therapy.

NITROFURANS—a *unique* class of antimicrobials

EATON LABORATORIES, NORWICH, NEW YORK


RAUDIXIN
THE CORNERSTONE OF
ANTIHYPERTENSIVE THERAPY
HELPS RELIEVE
THE PRESSURES
IN YOUR PATIENTS
HELPS RELIEVE
THE PRESSURES
ON YOUR PATIENTS
SUPPLY: 50 AND 100 MG. TABLETS, BOTTLES OF 100, 1000 AND 5000
SQUIBB
Squibb Quality – the Priceless Ingredient
Squibb Whole Root Rauwolfia Serpentina

relieve the tension—and control its G.I. sequelae

...Pathibamate®

meprobamate with PATHILON® tridihexethyl chloride Lederle

for relieving tension and curbing hypermotility and excessive secretion in G. I. disorders

PATHIBAMATE combines two highly effective and well-tolerated therapeutic agents:

meprobamate (400 mg. or 200 mg.)—a tranquilizer and muscle-relaxant widely accepted for the effective management of tension and anxiety

PATHILON (25 mg.)—an anticholinergic long noted for producing prompt symptomatic relief through peripheral, atropine-like action, yet with few side effects

now available...

Pathibamate-200 Tablets

200 mg. meprobamate • 25 mg. PATHILON

for more flexible control of G. I. trauma and tension smooth, sugar-coated, easy-to-swallow

PATHIBAMATE-400 and PATHIBAMATE-200 are indicated for duodenal ulcer; gastric ulcer; intestinal colic; spastic and irritable colon; ileitis; esophageal spasm; anxiety neurosis with gastrointestinal symptoms and gastric hypermotility.

Supplied: **PATHIBAMATE-400**—Each tablet (yellow, 1/2-scored) contains meprobamate, 400 mg.; PATHILON tridihexethyl chloride 25 mg.

PATHIBAMATE-200—Each tablet (yellow, coated) contains meprobamate, 200 mg.; PATHILON tridihexethyl chloride, 25 mg.

Administration and Dosage: **PATHIBAMATE-400**—1 tablet three times a day at mealtime and 2 tablets at bedtime.

PATHIBAMATE-200—1 or 2 tablets three times a day at mealtime and 2 tablets at bedtime.

Adjust dosage to patient response.

Contraindications: glaucoma; pyloric obstruction, and obstruction of the urinary bladder neck.

Lederle LEDERLE LABORATORIES, A Division of AMERICAN CYANAMID COMPANY, Pearl River, New York

In peptic ulcer,

five aids to comprehensive management

with **1** *preparation*

Added to the therapeutic regimen, ALUDROX SA simplifies your comprehensive management of the peptic-ulcer patient. With ALUDROX SA you can relieve the patient's pain, reduce his acid secretion, inhibit gastric motility, calm his emotional distress, and promote healing of his ulcer.

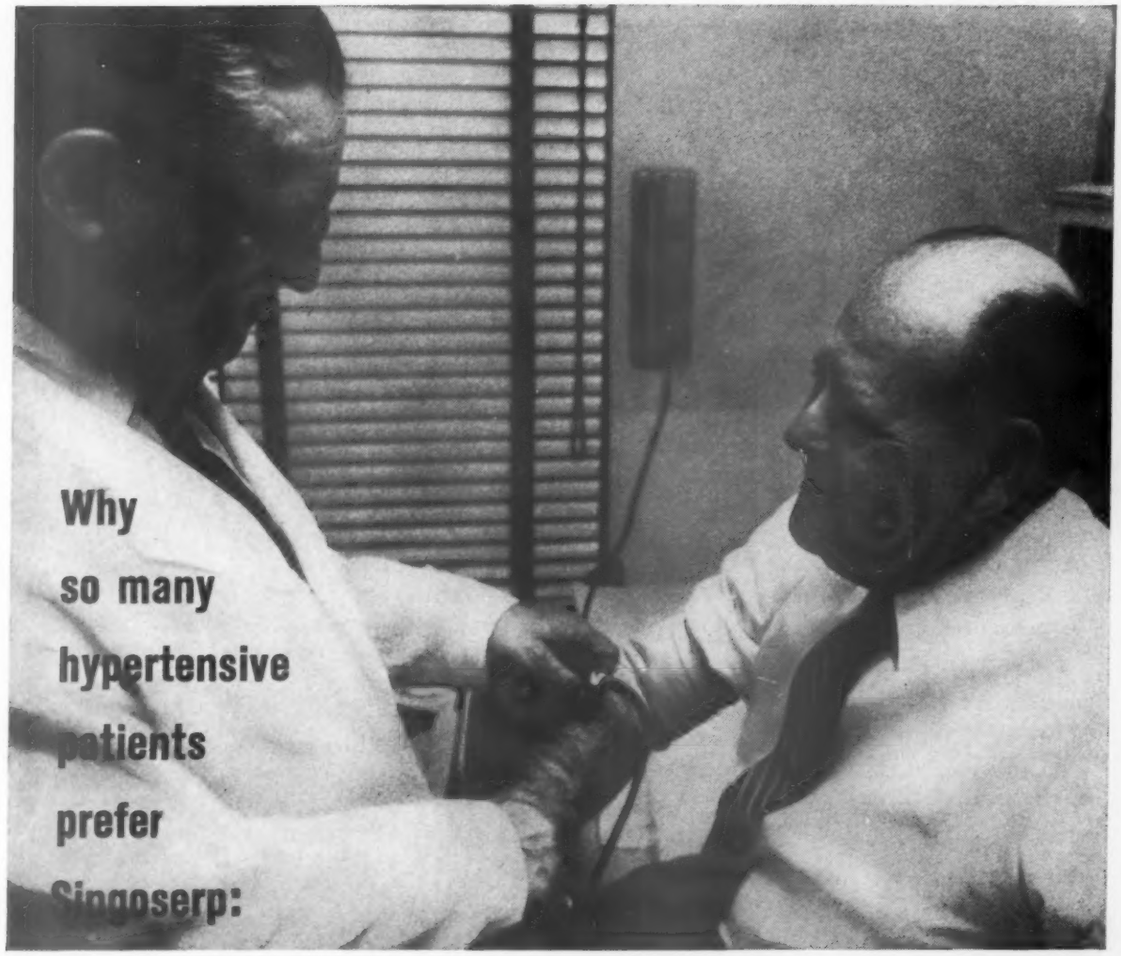
Ambutonium, an important new anticholinergic of demonstrated usefulness, is incorporated in ALUDROX SA to provide potent antisecretory and antimotility effects without significant side-reactions.

anticholinergic • antacid • sedative • anticonstipant • pepsin-inhibitor

ALUDROX® SA

Suspension and Tablets. Aluminum Hydroxide Gel with Magnesium Hydroxide, Ambutonium Bromide, and Butabarbital, Wyeth.

Wyeth®
Philadelphia 1, Pa.



It spares them from the usual rauwolfia side effects

FOR EXAMPLE: "A clinical study made of syrosingopine [Singoserp] therapy in 77 ambulant patients with essential hypertension demonstrated this agent to be effective in reducing hypertension, although the daily dosage required is higher than that of reserpine. Severe side-effects are infrequent, and this attribute of syrosingopine is its chief advantage over other Rauwolfia preparations. The drug appears useful in the management of patients with essential hypertension."*

*Herrmann, G. R., Vogelpohl, E. B., Hejtmancik, M. R., and Wright, J. C.: J.A.M.A. 169:1609 (April 4) 1959.

Remember SERPASIL® (reserpine CIBA) for the anxious hypertensive with or without tachycardia

Singoserp®

(syrosingopine CIBA)

First drug to try in new hypertensive patients

First drug to add in hypertensive patients already on medication

SUPPLIED: Singoserp *Tablets*, 1 mg. (white, scored); bottles of 100. Samples available on request. Write to CIBA, Box 277, Summit, N. J.

CIBA
SUMMIT, N. J.

2/2697MK

Tofrānil®
brand of imipramine HCl

The Dawn of a New Era in the Treatment of Depression

An entirely new compound originated in Geigy research laboratories, Tofrānil:

Exercises selective action on the symptoms of uncomplicated depression

Is effective in 70-85% of cases, particularly those of endogenous depression

Is frequently successful in even the most profound and chronic cases

Is virtually devoid of serious side reactions

Reduces the need for electro-convulsive therapy

May be administered by either oral or intramuscular routes

Indications for Tofrānil include:

Endogenous Depression, Reactive Depression, Involutional Melancholia, Senile Depression, Depression associated with other Psychiatric Disorders

Detailed literature on request

Availability:

Tofrānil® (brand of imipramine HCl); Sugar-coated, coral-colored tablets, 25 mg. each, in bottles of 100. Ampuls for intramuscular administration only, each containing 25 mg. in 2 cc. of solution (1.25 per cent) in cartons of 10 and 50.

Selected Bibliography:

1. Ayd, F. J., Jr.: Bulletin of School of Medicine, University of Maryland 44:29, 1959. 2. Azima, H.: Canad. M.A.J. 80:535, 1959. 3. Azima, H., and Vispo, R. H.: Am. J. Psychiat. 115:459, 1958. 4. Kuhn, R.: Am. J. Psychiat. 115:459, 1958. 5. Lehmann, H. E.; Cahn, C. H., and de Verteuil, R. L.: Canad. Psychiat. A. J. 3:155, 1958. 6. Mann, A. M., and MacPherson, A. S.: Canad. Psychiat. A. J. 4:38, 1959. 7. Sloane, R. B.; Habib, A., and Batt, U. E.: Canad. M.A.J. 80:540, 1959. 8. Straker, M.: Canad. M.A.J. 80:546, 1959.

Geigy, Ardsley, New York

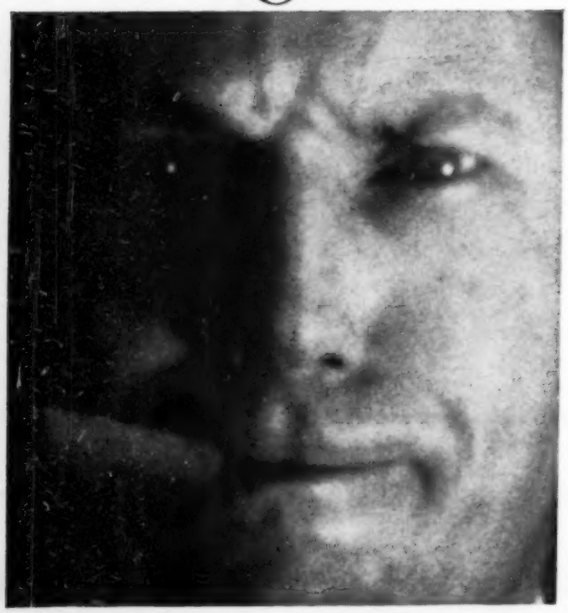
05659 B

potent
and unique thymoleptic agent

Geigy

In HYPERTENSION change to MODERIL® brand of rescinnamine for better management

the rewards of reserpine



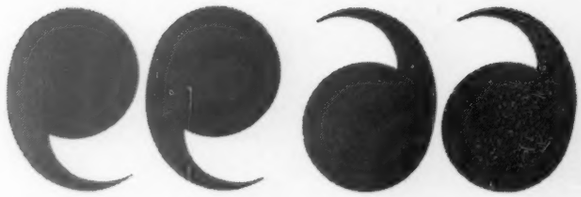
Gradual, sustained lowering of blood pressure

Effective alone in mild to moderate labile hypertension

Adjunctive therapy in severe hypertension, cutting dosage requirements and side effects of other agents

DOSAGE: Up to 0.5 mg. daily for 2 weeks; then adjust to patient response.

Supplied: Tablets, 0.25 mg. (yellow) and 0.5 mg. (salmon).



"as effective an hypotensive agent as reserpine... producing less side effects"[1]

"a safe, easily tolerated agent for chronic drug administration..."[2]

"produces less sedation and less bradycardia in proportion to its hypotensive dose than does reserpine."[3]

"Reserpine produces more weakness, fatigue, and sedation... In this series reserpine produced mental depression in a number of cases, and this was not observed with rescinnamine [MODERIL]*..."*[4]

"Sedation and bradycardia, in particular, appear to occur less frequently and in mild form with rescinnamine."[5]

"mild depressions, nightmares or excessive drowsiness have been relieved on transfer to equally hypotensive doses of... rescinnamine. The increase of appetite that often follows the administration of reserpine has been lacking and even replaced by decrease of appetite on transfer to rescinnamine."[6]

"rescinnamine has less slowing effect on the heart than does reserpine and apparently has less gastrointestinal effect."[2]

"the addition of rescinnamine reduced the need for high doses of ganglion-blocking agents."[1]

without its penalties

MODERIL—a purified alkaloid of Rauwolfia—lessens the frequency and severity of reserpine side effects,[1-10] *such as:*

sedation • bradycardia • mental depression • weakness • fatigue • lassitude • sleepiness • nightmares • gastrointestinal effects

MODERIL BIBLIOGRAPHY 1. Winton, S. S.: Internat. Rec. Med. 170:665, 1957. 2. Hershberger, R. L.; Dennis, E. W., and Moyer, J. H.: Am. J. M. Sc. 231:542, 1956. 3. Moyer, J. H.: A. M. A. Arch. Int. Med. 96:518, 1955. 4. Moyer, J. H.; Dennis, E., and Ford, R.: Ibid. p. 530. 5. Council on Drugs, A. M. A.: New and Nonofficial Drugs 1959, Philadelphia, Lippincott, 1959, p. 374. 6. Smirk, F. H.: Postgrad. Med. 25:11, 1959. 7. Moyer, J. H., et al.: South. M. J. 50:499, 1957. 8. Malamud, W., et al.: Am. J. Psychiat. 114:193, 1957. 9. Smirk, F. H., and McQueen, E. G.: Lancet 2:115, 1955. 10. Malitz, S.: J. Chron. Dis. 9:278, 1959.

Pfizer *Science for the world's well-being*

PFIZER LABORATORIES, Brooklyn 6, N. Y.
Division, Chas. Pfizer & Co., Inc.

Why Claysorb means more effective antidiarrheal treatment

The response to an antidiarrheal preparation is directly linked to the effectiveness of its adsorbent. In both POLYMAGMA and POLYMAGMA Plain, the new agent Claysorb* gives you a previously unattainable adsorptive power . . . proved to be five times beyond that of kaolin in removing diarrhea-causing toxins. In addition, POLYMAGMA and POLYMAGMA Plain protect the irritated intestinal walls, promote well-formed stools, help restore healthy intestinal function.

POLYMAGMA
For bacterial diarrhea—
bactericidal against many pathogens

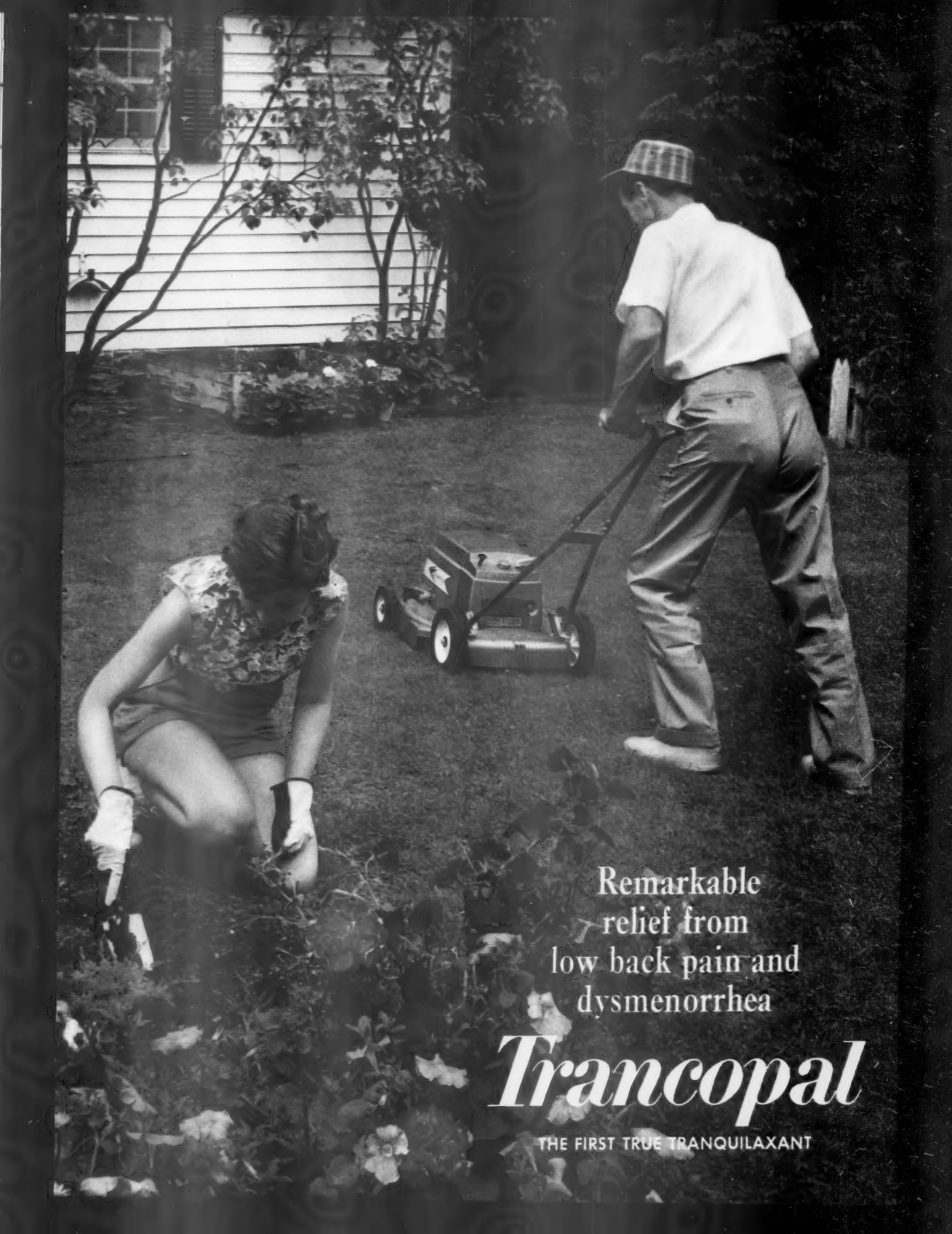
POLYMAGMA Plain
For nonbacterial diarrhea—
same formula but without antibiotics

Polymagma®

Dihydrostreptomycin Sulfate, Polymyxin B Sulfate, and Pectin with Claysorb* (Activated Attapulgite, Wyeth) in Alumina Gel

**Trademark*

Wyeth®
Philadelphia 1, Pa.


Remarkable
relief from
low back pain and
dysmenorrhea
Trancopal
THE FIRST TRUE TRANQUILAXANT

Here is what you can expect when you prescribe

for low back pain

case profile no. 2758*

A middle-aged man had intermittent low back pain attributed to injuries received in an automobile accident three years ago. The pain radiated down both legs, making the patient walk bent over. He also had difficulty in getting out of bed and had to pull his knees up and roll out. Any heavy lifting precipitated a new attack, and he tired easily.

Findings on x-ray of the thoracic and lumbar spine were negative. All other laboratory studies were within normal limits. A herniated disc, though still a possibility, was temporarily ruled out by the neurologic examination. Previous treatment consisted of analgesics, steroids (without success), and narcotics during severe attacks.

On a dosage of Trancopal, 100 mg. t.i.d., this patient is able to walk around almost normally and carry on his regular activities as long as he does not overdo. He has received Trancopal for over seven months with excellent relief of symptoms. There have been no side effects.

**Clinical Reports on file at the Department of Medical Research, Winthrop Laboratories.*

what you
when you

THE FIRST TRUE TRANQUILAXANT

Trancopal®

for dysmenorrhea
and premenstrual tension

case profile no. 3347*

A 35-year-old housewife had a history of severe dysmenorrhea and premenstrual tension. Menarche occurred at the age of 14. She is a gravida 2, para 1. Her menstrual cycle is fairly regular, and previous medical history indicates no apparent abnormalities. Findings on pelvic examination were negative. Severe tension and irritability routinely occurred from two to seven days before and during menstruation. Cramping was experienced for all three days of the menstrual period. Analgesic preparations provided limited symptomatic relief.

Trancopal, 200 mg. t.i.d., was prescribed for dysmenorrhea. It not only has relieved the severe cramping, but has provided a welcome relief from the irritability accompanying it. Because of these excellent results, Trancopal also was prescribed for her tenseness during the premenstrual period with a most gratifying response.

This patient has successfully remained on the above regimen for over six months without adverse effects.

Turn Page for Complete Listing of Indications and Dosage

THE FIRST TRUE TRANQUILAXANT

Trancopal

potent muscle relaxant

effective tranquilizer

- In musculoskeletal disorders, effective in 91% of patients.[1]
- In anxiety and tension states, effective in 88% of patients.[1]
- Low incidence of side effects (2.3% of patients). Blood pressure, pulse rate, respiration and digestive processes unaffected by therapeutic dosage. No effects on hematopoietic system or liver and kidney function.
- No gastric irritation. Can be taken before meals.
- No clouding of consciousness, no euphoria or depression.

Indications:

Musculoskeletal:
Low back pain (lumbago, etc.)
Neck pain (torticollis, etc.)
Bursitis
Rheumatoid arthritis
Osteoarthritis
Disc syndrome
Fibrositis
Ankle sprain, tennis elbow, etc.
Myositis
Postoperative muscle spasm

Psychogenic:
Anxiety and tension states
Dysmenorrhea
Premenstrual tension
Asthma
Angina pectoris
Alcoholism

Trancopal Caplets®:
100 mg. (peach colored, scored), bottles of 100.

Dosage: Adults, 100 or 200 mg. orally three or four times daily. Relief of symptoms occurs in fifteen to thirty minutes and lasts from four to six hours.

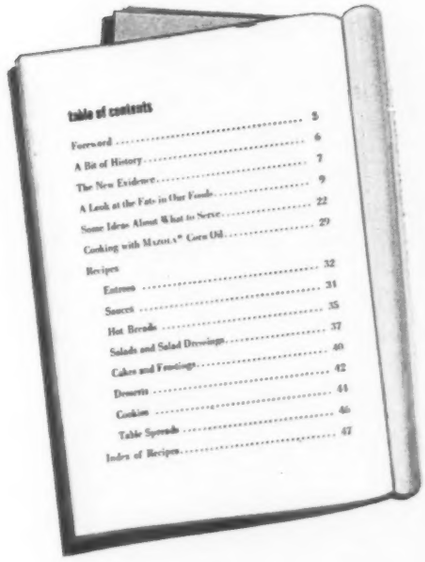
1. Collective Study, Department of Medical Research, Winthrop Laboratories.

Winthrop LABORATORIES
New York 18, New York

Trancopal (brand of chlormezanone) and Caplets, trademarks reg. U.S Pat. Off. Printed in U.S.A. 6-59 (1385M)

AND DOCTOR...
"Do I have to go on a fat-free diet?"

"Can you give me a meal plan?"



"Which fats can I eat?"

"How about cooking with oils"

New menu book acts as "answering service" for patients with cholesterol problems

As a Major Aid to your own personal contact in cases where dieting for cholesterol control is indicated, we have recently published "Cooking For Health With Mazola Corn Oil." This comprehensive and authoritative book provides patients with detailed information on relative amounts of unsaturated and saturated fats in many foods, plus many tempting recipes, practical assistance in meal planning and easy-to-read tables on food values in terms of fat calories—all devoted to saving your time and building patients' acceptance of meal planning for low saturated-fat intake.

Because it answers so many of your patients' questions—simply and accurately—because it provides a *wealth* of useful information *which so few doctors have time to provide*—you'll want to see that each of your "cholesterol-conscious" patients receives a copy.

For your copy of "Cooking For Health With Mazola Corn Oil" plus a supply of postage-free cards with which your patients may order theirs, simply send us the coupon below.

NEW CONCEPTS OF THE VALUE OF CORN OIL TO HEALTH

Clinical studies with controlled diets have demonstrated that corn oil can be effective in lowering serum cholesterol levels. Investigators have variously ascribed this action of corn oil to total unsaturation, linoleic acid, sitosterols and other active components not as yet identified.

For convenience, we propose to refer to this combination as the "L-plus" factor. Of all leading U.S. Brands, only Mazola is pure Corn Oil. Rich in "L-plus" factor, Mazola is ideal in dietary treatment of hypercholesterolemia.

Cooking for Health with Mazola Corn Oil

CORN PRODUCTS COMPANY, Dept. A
120 Brighton Road
Clifton, N. J.

Please send me a copy of "Cooking For Health With Mazola Corn Oil" plus a supply of order cards for my patients.

Name _____

Address _____

City _____ *Zone* _____ *State* _____

Technical Pamphlet "Facts About Mazola Corn Oil" also available. Provides technical information on chemical and physical properties. Check here ☐ if you wish a copy of this pamphlet.

CORN PRODUCTS COMPANY

Whether the response in

acute skeletal muscle spasm

is *"marked"*[1]

"pronounced"[2]

"excellent"[3]

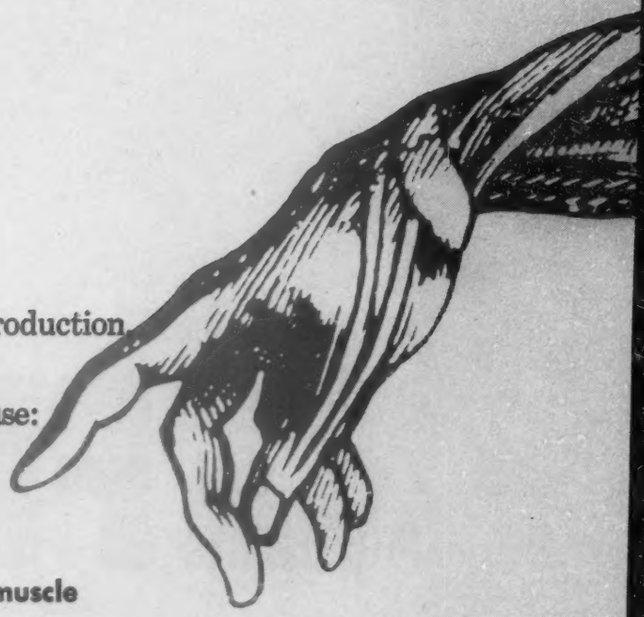
"significant"[4]

or *"gratifying"*[5]—

it all adds up to

94.4% beneficial results with

RO



In the comparatively short period since its introduction, ROBAXIN has become the leader in prescription preference for skeletal muscle relaxation, because:

- **It is highly potent—and long acting.**[1,2]
- **It is relatively free of adverse side effects.**[1,2,4,5]
- **In ordinary dosage, it does not reduce normal muscle strength or reflex activity.**[1]

ROBAXIN's outstanding effectiveness is authenticated by the results of five recent clinical studies in which it was administered to 198 patients.[1,2,3,4,5] Good results were reported in 80.3% of the patients and moderate results in 14.1%—or an over-all beneficial effect in 94.4%. Conditions treated included spasm secondary to trauma, ligamentous strains, herniated disc, torticollis, whiplash injury, contusions, fractures, fibromyositis, acute myalgic disorders, and skeletal muscle spasms afflicting industrial workers.

Supply: ROBAXIN Tablets, 0.5 Gm. (white, scored) in bottles of 50.

References:

1. Carpenter, E. B.: Southern M. J. 51:627, 1958. **2.** Forsyth, H. F: J.A.M.A. 167:163, 1958. **3.** O'Doherty, D. S., and Shields, C. D.: J.A.M.A. 167:160, 1958. **4.** Park, H. W.: J.A.M.A. 167:168, 1958. **5.** Plumb, C. S.: Journal-Lancet 78:531, 1958.

Robins

baxin®

Methocarbamol Robins, U.S. Pat. No. 2770649

A. H. ROBINS CO., INC., RICHMOND 20, VIRGINIA

Ethical Pharmaceuticals of Merit since 1878

for your G.U. patients **FREEDOM**

FURADANTIN®

brand of nitrofurantoin

IN SEVEN YEARS NEGLIGIBLE DEVELOPMENT OF BACTERIAL RESISTANCE WITH FURADANTIN

from pain, infection and drug-induced complications

FREEDOM FROM PAIN AND INFECTION

"Nitrofurantoin [FURADANTIN] was effective clinically, with a pronounced improvement, indicated by the appearance of the urine as well as by verbal commendation by the patient, within 24 to 36 hours. . . . Some of these patients with seemingly impossible cases were cured of their infection."[1]

"During the initial week of therapy, when the dose of nitrofurantoin was 100 mg. four times a day, the urine became free of pus and bacteria. Symptoms of urinary frequency, urgency, and dysuria were relieved."[2]

FREEDOM FROM DRUG-INDUCED COMPLICATIONS

- No significant development of bacterial resistance in over 7 years.
- No irreversible toxic effects on kidneys, liver, blood-forming organs or central nervous system ever reported.
- No monilial superinfection or staphylococcic enteritis ever reported.
- No fatalities from FURADANTIN therapy; the margin of safety is 90 to 1.
- "The drug was given continuously and safely for as long as three years."[2]

"FURADANTIN has characteristics that make it a valuable drug for long-term administration to control urinary tract infection. These include its lack of toxicity, wide range of antibacterial effectiveness, and reduced tendency to induce development of bacterial resistance to the drug."[3]

AVERAGE FURADANTIN ADULT DOSAGE: One 100 mg. tablet q.i.d. taken with meals and at bedtime with food or milk. Available as Tablets, 50 and 100 mg.; Oral Suspension, 25 mg. per 5 cc. tsp.

REFERENCES: 1. Stewart, B. L., and Rowe, H. J.: J. Am. M. Ass. 160:1221, 1956. 2. Lippman, R. W., et al.: J. Urol., Balt. 80:77, 1958. 3. Marshall, M., Jr., and Johnson, S. H., III: J. Am. M. Ass. 169:919, 1959.

NITROFURANS—a *unique* class of antimicrobials—neither antibiotics nor sulfonamides

EATON LABORATORIES, NORWICH, NEW YORK

MR. COBB:
And those are the three reasons for prescribing AMPLUS IMPROVED for the control of obesity.

DR. M.:
Mr. Cobb, if you were as convincing with your wife as you just were with me, you wouldn't be here today.

new AMPLUS® improved

(D-AMPHETAMINE + ATARAX® + VITAMINS AND MINERALS)

One capsule half-hour before each meal. Bottles of 100 soft, soluble capsules, this actual size.

MR. COBB DETAILS DR. M.

DR. M.: What's this, nurse? Gordon Cobb, the Roerig detail man, here as a patient? Send him in, please.

MR. COBB: **Don't get the wrong idea about this black eye, Doctor. All I said to the missus was, "Dear, perhaps AMPLUS IMPROVED might help you reduce a little." And WHOMP—**

DR. M.: Well, I can understand her side of the issue, too. I always broach the subject of reducing with utmost finesse.

MR. COBB: **So did I! First I told her that notable progress had been made in anorexigenic agents—as, for example, the addition of vitamins and minerals to d-amphetamine. You remember—that was AMPLUS.**

DR. M.: Naturally. I prescribed it quite frequently. Kept mineral and vitamin requirements up during dieting.

MR. COBB: **OK. So then I mentioned the "improvement" part of AMPLUS IMPROVED—tranquilizing with ATARAX.**

DR. M.: Good addition. ATARAX reduces any undue nervous stimulation.

MR. COBB: **Also reduces the gastric craving because it's antisecretory.**

DR. M.: Gordon, you're mixing business with malaise.

MR. COBB: **Anyway, she hauls off like Dempsey and here I am.**

DR. M.: Mr. Cobb, if you were as diplomatic with your wife as you just were in convincing me to prescribe AMPLUS IMPROVED, you wouldn't be here today.

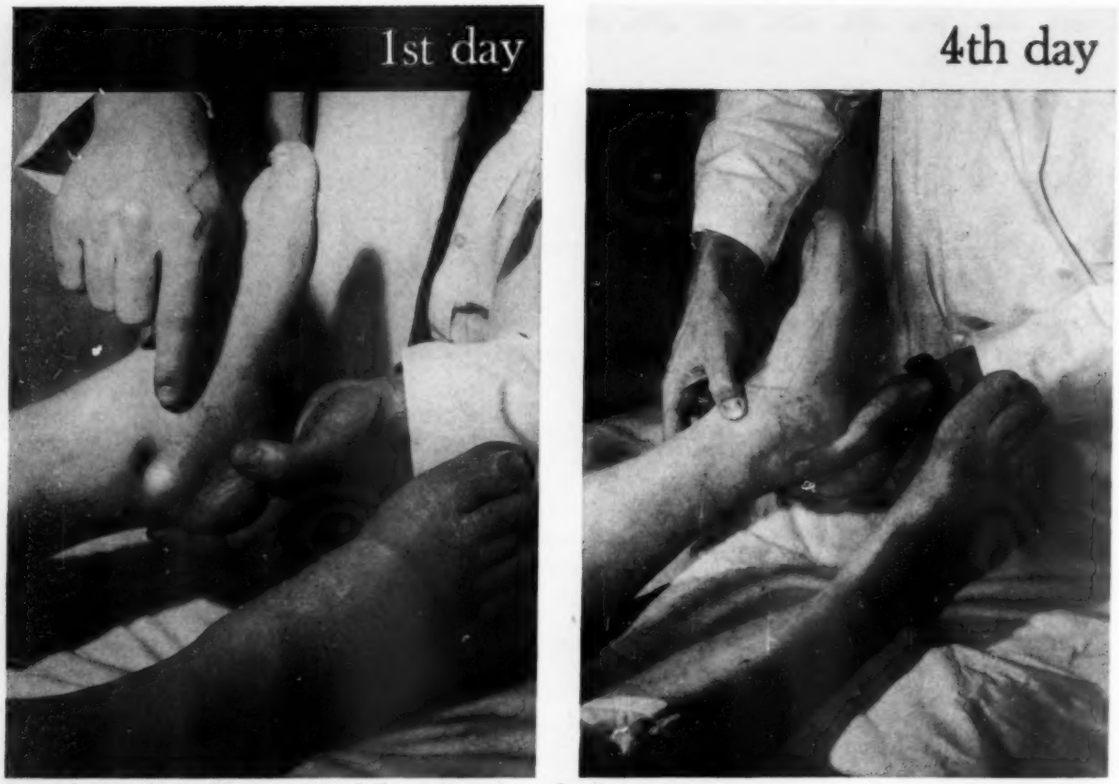
MR. COBB: **Maybe so, Doctor. But you know the saying, "no pains—no gains."**

DR. M.: True. So here are two prescriptions:
for your "pains"—hot and cold applications;
for your wife's "gains"—AMPLUS IMPROVED.

representing
J. B. Roerig and Company
Mr. Cobb

ROERIG Rx

New York 17, N. Y.
Division, Chas. Pfizer & Co., Inc.
Science for the World's Well-Being



Record of patient with congestive failure, treated at a leading Philadelphia hospital. Photos used with permission of the patient.

marked pitting edema (4+) cleared in 4 days with Esidrix

Highest fluid yields, lowest blood-pressure levels yet achieved with oral diuretic-antihypertensive therapy.

Indicated in:

congestive heart failure
hypertension
hypertensive vascular disease
premenstrual edema
toxemia of pregnancy
edema of pregnancy
steroid-induced edema
nephrosis
nephritis

C I B A SUMMIT, N. J.

DOSAGE: Esidrix is administered orally in an average dose of 75 to 100 mg. daily, with a range of 25 to 200 mg. A single dose may be given in the morning or tablets may be administered 2 or 3 times a day.

SUPPLIED: *Tablets,* 25 mg. (pink, scored); bottles of 100 and 1000. *Tablets,* 50 mg. (yellow, scored); bottles of 100 and 1000.

2/2695MK

remember

Serpasil® (reserpine CIBA) for the anxious hypertensive with or without tachycardia

L.S., 81-year-old patient with complaint of painless hematuria admitted to hospital on 3/3/59. Past history included congestive heart failure of 15 years' duration. **Clinically significant symptoms:** expiratory wheezes over entire chest; bilateral coarse rales of both bases; slight abdominal distention (without evidence of ascites); palpable liver 2-3 fingerbreadths below rib cage; bilateral pitting edema (4+) of pretibial and ankle areas. **Admission diagnosis:** hematuria of unknown origin; arteriosclerotic cardiovascular disease; poorly compensated heart failure; chronic pulmonary fibrosis with pulmonary insufficiency.

Patient was put on regimen of bed rest, moderate salt restriction, digitalis and pulmonary decongestants. When ankle edema, hepatic congestion and rales failed to clear by 3/6, Esidrix 50 mg. b.i.d. was ordered. By 3/8 L.S. had lost 3 pounds. Rales decreased; there was 1+ pitting edema of ankle area only. He felt more comfortable, was able to enjoy reading newspapers and magazines in bed.

Ambulatory on the 4th day of Esidrix therapy, L.S. visited his neighbors down the hall, played checkers with another patient. There was no evidence of ankle edema. By 3/11, patient's weight had dropped 2 more pounds and rales were gone. Patient tolerated cystoscopy and fulguration of a small bleeding polyp in his bladder on 3/12 very well. On 3/14 he was discharged.

Patient L.S. Date	3/4	3/5	3/6	3/7	3/8	3/9	3/10	3/11	3/12	3/13
Urinary Output (ml.)	840	690	960	2140	1230	660	1220	1350	--	--
Weight (lbs.)	139	--	--	--	136	--	--	134	--	--
Esidrix Dosage (mg./day)	0	0	50	100	100	100	100	100	50	100

Esidrix T.M.

(hydrochlorothiazide CIBA)

- **relieves edema in many patients refractory to other diuretics[1]**
- **often produces greater weight loss than parenteral mercurials or chlorothiazide[2]**
- **provides a greater average reduction in blood pressure than chlorothiazide[3]**
- **is exceptionally safe . . . reduces the likelihood of electrolyte imbalance**

1. Brest, A. N., and Likoff, W.: Am. J. Cardiol. 3:144 (Feb.) 1959. 2. Clark, G. M.: Clinical report to CIBA.
3. Dennis, E. W.: Clinical report to CIBA.

2/2684MX-2

THE CREST OF LEADERSHIP

MEDICAL JOURNALS are the first working tool of the researcher and trail-blazer in effecting new technics and therapy. The accomplishments of the earlier workers are perpetuated in the printed records of the past and present and serve as a basis for future developments.

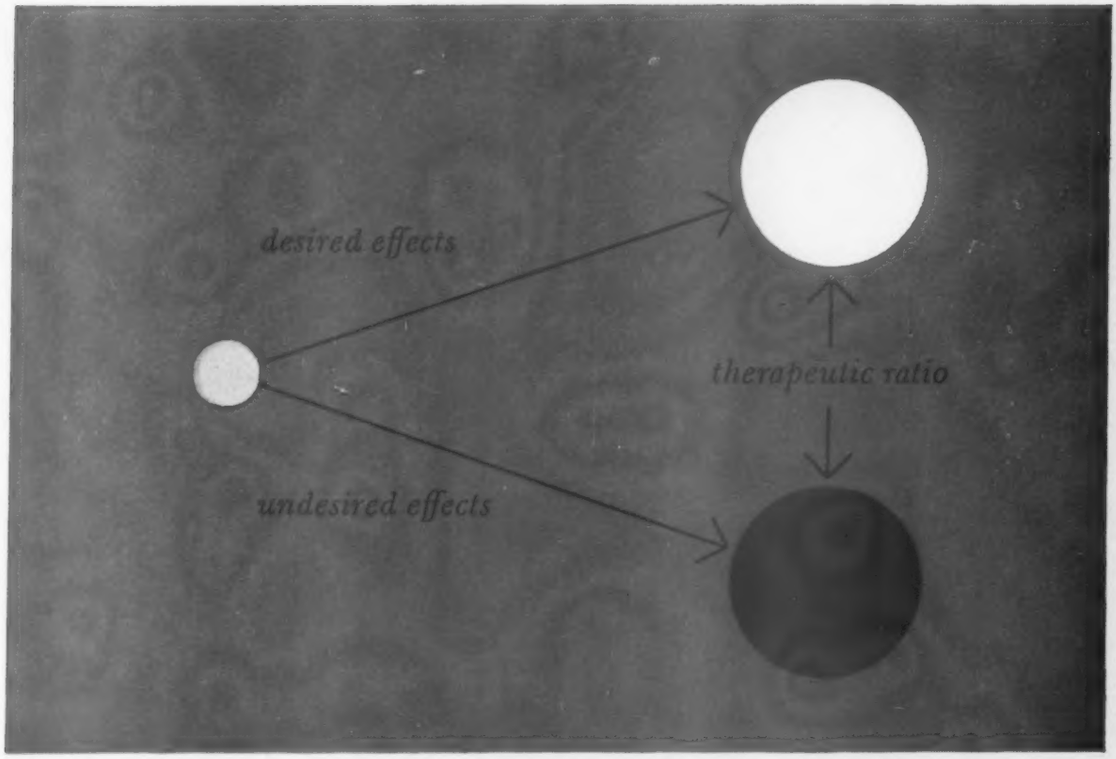
YORKE PUBLICATIONS by its planned seminars and symposia enrich the knowledge and enlarge the field of effectiveness of the American physician in guarding the health of our country's population. Exhaustive studies on vital and pertinent subjects are prepared by eminent leaders and are recorded as soon as possible in the pages of the respective YORKE JOURNALS.

Recognizing the prestige and loyal readership enjoyed by the YORKE PUBLICATIONS, leaders in the pharmaceutical industry use these journals for carrying their advertising messages to the moulders of opinion and action.

YORKE PUBLISHING CO.

NEW YORK, N. Y.

THE AMERICAN JOURNAL OF SURGERY
THE AMERICAN JOURNAL OF MEDICINE
THE AMERICAN JOURNAL OF CLINICAL NUTRITION
THE AMERICAN JOURNAL OF CARDIOLOGY
MODERN DRUGS

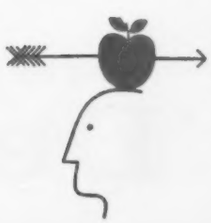


The best therapeutic ratio in the steroid field confirmed by a comparative clinical study of

prednisone
prednisolone
methylprednisolone
triamcinolone
dexamethasone

in 65 rheumatoid arthritis patients:

". . . It would appear from these comparative observations that methylprednisolone [Medrol] probably is the steroid of choice for initial trial in a patient with rheumatoid arthritis. It is potent, and displays a slightly improved 'safety' record, showing a reduced frequency of disturbing side effects compared with the other steroids."[1]



Medrol

TRADEMARK, REG. U. S. PAT. OFF. — METHYLPREDNISOLONE, UPJOHN

...hits the disease, but spares the patient

1. Neustadt, D. H.: Corticosteroid Therapy in Rheumatoid Arthritis: Comparative Study of Effects of Prednisone and Prednisolone, Methylprednisolone, Triamcinolone and Dexamethasone, J.A.M.A., in press.

Upjohn

"I seem to have the blues all the time...
I can't sleep..."

in the depressed, unhappy patient

PROMPTLY IMPROVES MOOD

without excitation

- **Acts fast to relieve depression and its common symptoms:** sadness, crying, anorexia, listlessness, irritability, rumination, and insomnia.
- **Restores normal sleep**—without hang-over or depressive aftereffects. Usually eliminates need for sedative-hypnotics.

EFFICACY AND SAFETY CONFIRMED IN OVER 3,000 DOCUMENTED CASE HISTORIES.[1,2,3]

Dosage: Usual starting dose is 1 tablet q.i.d. When necessary, this dose may be gradually increased up to 3 tablets q.i.d.

Composition: Each light-pink, scored tablet contains 1 mg. 2-diethylaminoethyl benzilate hydrochloride (benactyzine HCl) and 400 mg. meprobamate.

References:

1. Alexander, L.: J.A.M.A. 166:1019, March 1, 1958.
2. Current personal communications; in the files of Wallace Laboratories.
3. Pennington, V.M.: Am. J. Psychiat. 115:250, Sept. 1958.

for depression

▲Deprol▲†

©WALLACE LABORATORIES, *New Brunswick, N. J.*

†TRADE-MARK

CD-9182

"... which antacid? Rorer's Maalox. Excellent results, no constipation plus a pleasant taste that patients like."

MAALOX® an efficient antacid suspension of magnesium-aluminum hydroxide gel offered in bottles of 12 fluidounces.

TABLET MAALOX: 0.4 Gram (equivalent to one teaspoonful), Bottles of 100.

TABLET MAALOX No. 2: 0.8 Gram, double strength (equivalent to two teaspoonfuls), Bottles of 50 and 250.

Samples on request.

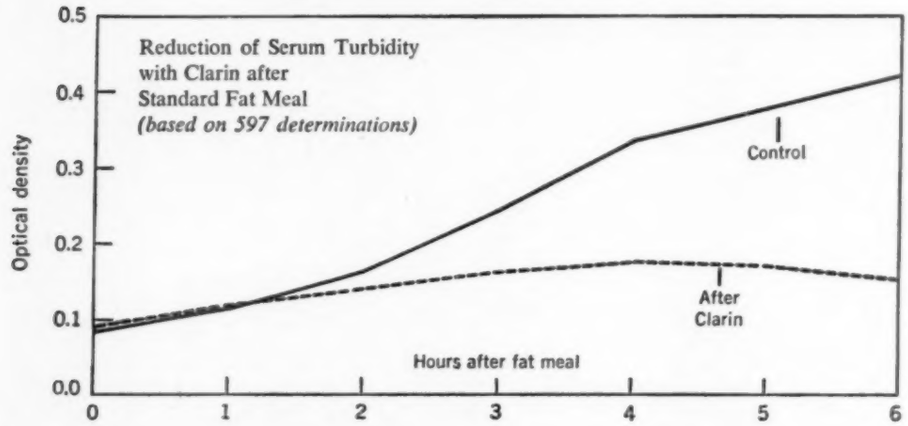
WILLIAM H. RORER, INC., Philadelphia 44, Pennsylvania

in the management of atherosclerosis

Clarin*

(sublingual heparin potassium, Leeming)

clears lipemic serum



Each time your patients eat a substantial fat-containing meal, lipemia results. Small amounts of injected heparin will help control this increased fat content in the blood,[1,2] but widespread adoption of this method has been hampered by its inconvenience, pain, cost and the necessity for periodic checks on blood clotting time.

Now, long-term preventive heparin therapy is practical for the first time with the introduction of CLARIN—which is heparin in *sublingual* form. Each CLARIN tablet contains 1500 I.U. of heparin potassium—a sufficient amount to clear lipemic serum without affecting coagulation mechanisms.[3,4]

With one mint-flavored CLARIN tablet under the tongue after each meal, lipemia is regularly controlled, removing a constant source of danger to the atherosclerotic patient. He may eat safely, with less fear of dangerous results, without hard-to-follow diets.

The varied implications of CLARIN in beneficially affecting fat metabolism are obviously far-reaching. The relationship between heparin, lipid metabolism and atherosclerosis may well be analogous to that between insulin, carbohydrate metabolism and diabetes mellitus.[5]

Use CLARIN to protect your atherosclerotic patients—the postcoronaries and those with early signs of coronary artery disease.

Indication: For the management of hyperlipemia associated with atherosclerosis.

Dosage: After each meal, hold one tablet under the tongue until dissolved.

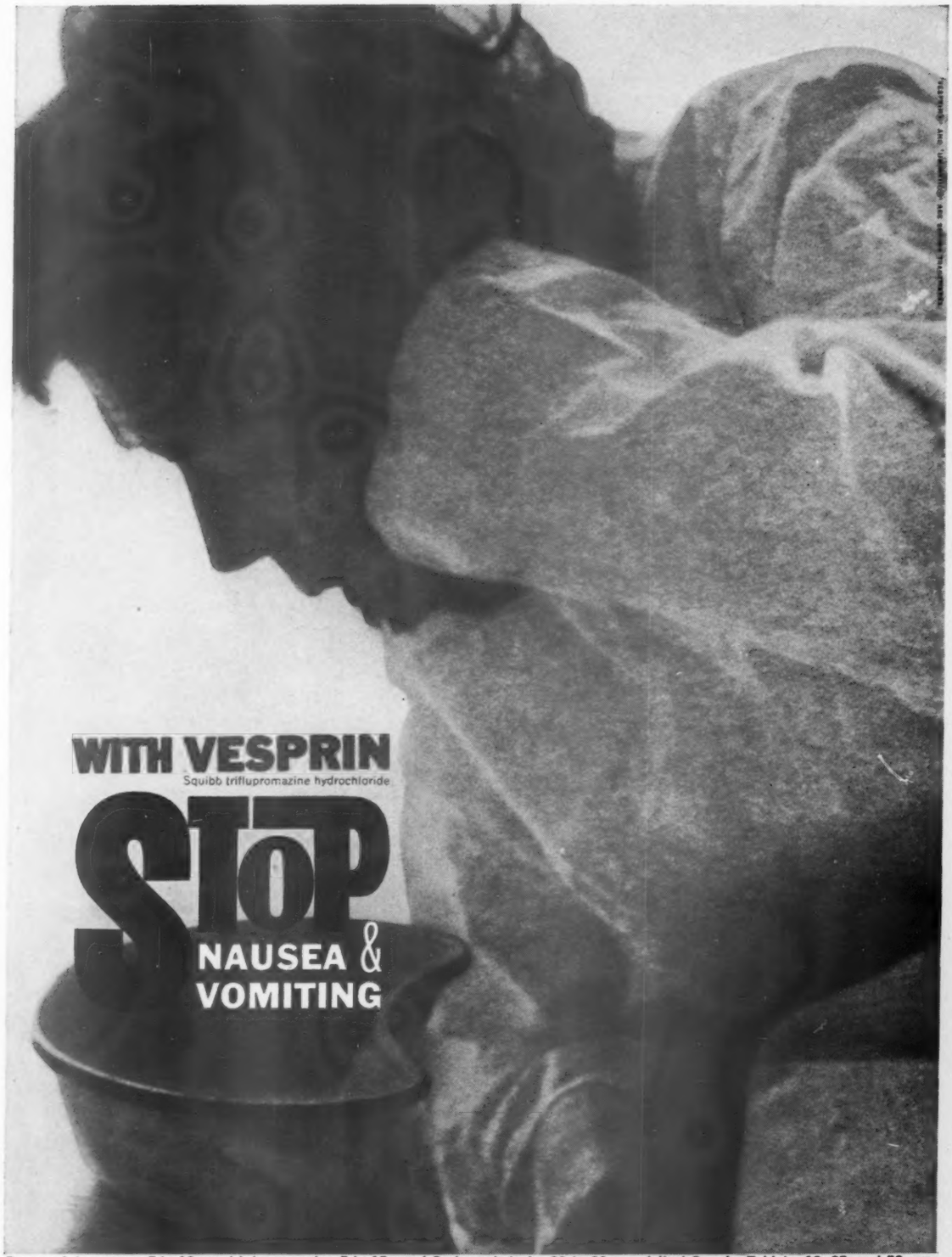
Supplied: In bottles of 50 pink, sublingual tablets, each containing 1500 I.U. heparin potassium.

1. Council on Drugs, J.A.M.A. *166*:52 (Jan. 4) 1958. 2. Hahn, P. F.: Science *98*:19 (July 2) 1943. 3. Fuller, H. L.: Angiology *9*:311 (Oct.) 1958. 4. Rubio, F. A., Jr.: Personal communication. 5. Engelberg, H., *et al.*: Circulation *13*:489 (April) 1956.

*Trade Mark. Patent applied for.

Thos. Leeming & Co., Inc.

155 East 44th Street, New York 17, N. Y.

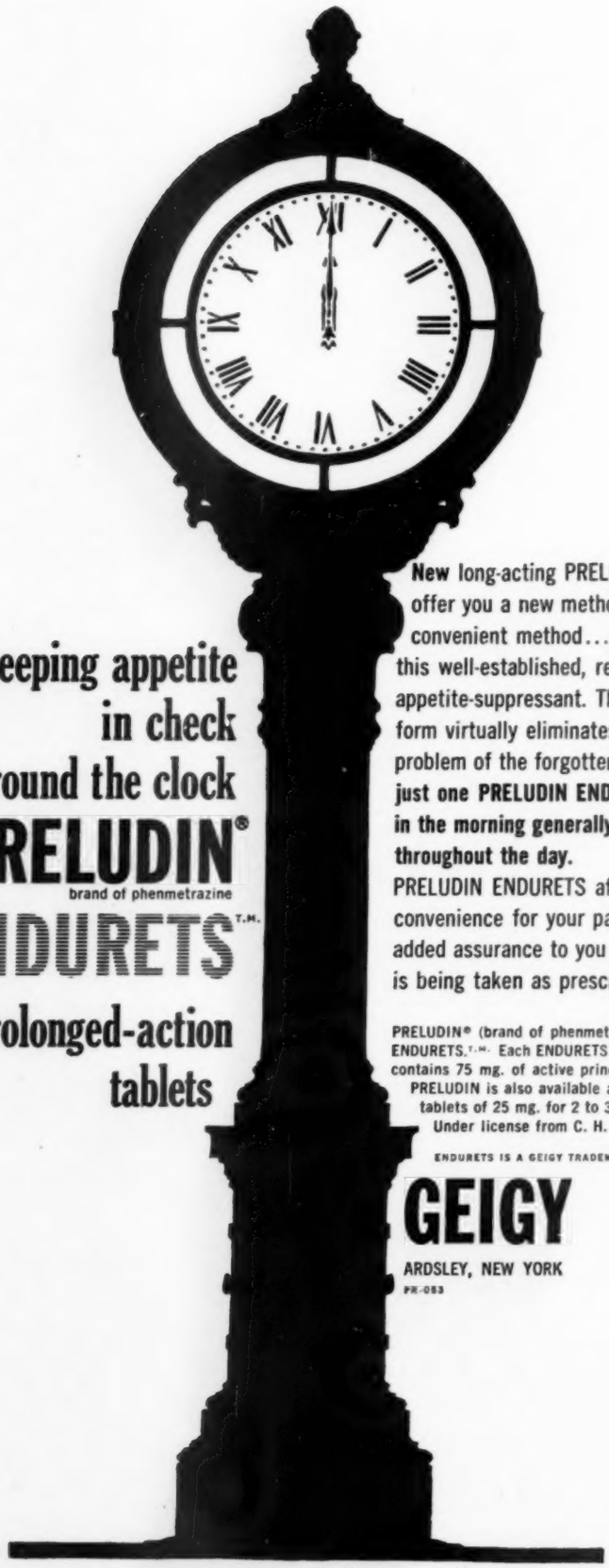


Dosage: Intravenous, 5 to 12 mg. / Intramuscular, 5 to 15 mg. / Oral prophylaxis, 20 to 30 mg. daily / **Supply:** Tablets, 10, 25, and 50 mg., bottles of 50 and 500 / Emulsion, 30-cc. dropper bottles and 120-cc. bottles (10 mg./cc.) / Parenteral Solution, 1-cc. multiple dose vial (20 mg./cc.) / 10-cc. multiple dose vial (10 mg./cc.) / Vesprin Injection Unimatic (15 mg. in 0.75 cc.)

Vesprin/the tranquilizer that fills a need in every major area of medical practice/ anxiety and tension states, pre- and postoperative tranquilization, alcoholism, and obstetrics.

SQUIBB

Squibb Quality – the Priceless Ingredient



keeping appetite
in check
around the clock

PRELUDIN®
brand of phenmetrazine

ENDURETS™

prolonged-action
tablets

New long-acting PRELUDIN ENDURETS offer you a new method...a more convenient method...of administering this well-established, reliable appetite-suppressant. The new ENDURETS form virtually eliminates the vexing problem of the forgotten dose because... **just one PRELUDIN ENDURET taken in the morning generally curbs the appetite throughout the day.**

PRELUDIN ENDURETS afford greater convenience for your patient... added assurance to you that medication is being taken as prescribed.

PRELUDIN® (brand of phenmetrazine hydrochloride) ENDURETS.™ Each ENDURETS prolonged-action tablet contains 75 mg. of active principle.

PRELUDIN is also available as scored, square pink tablets of 25 mg. for 2 to 3 times daily administration.

Under license from C. H. Boehringer Sohn, Ingelheim.

ENDURETS IS A GEIGY TRADEMARK

GEIGY

ARDSLEY, NEW YORK

PR-053

Back Issues Wanted

(MUST BE IN GOOD CONDITION)

THE AMERICAN JOURNAL OF MEDICINE

will pay $1.00 per copy for the following issues:

January 1948	June 1957
July 1948	August 1957
September 1948	September 1957
February 1954	November 1957
May 1955	December 1957
August 1955	May 1958
September 1955	August 1958
May 1957	

Send Postpaid to

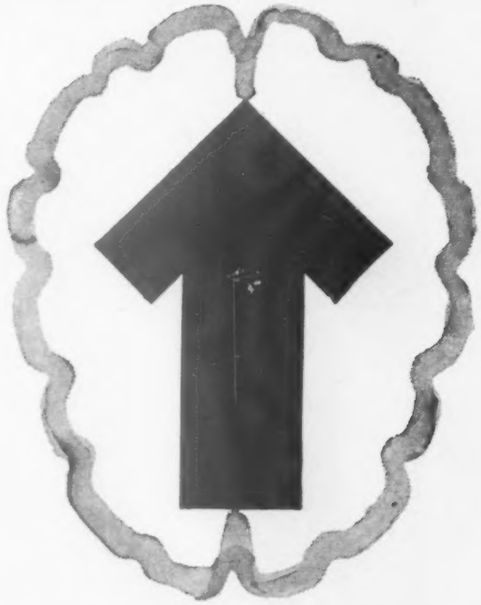
The American Journal of Medicine, Inc.

11 East 36th Street, New York 16, N. Y.

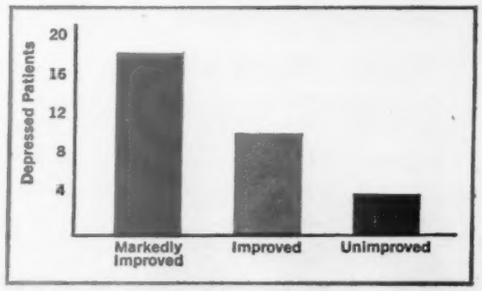
new psychoactive agent

Catron®

β-phenylisopropyl hydrazine supplied as the hydrochloride



Revitalizes depressed patients—elevates mood, increases alertness and ability to maintain work and social adjustment.[1,2]



1. Agin, H. V.: in A Pharmacologic Approach to the Study of the Mind, Springfield, Ill., Charles C Thomas, in press.
2. Agin, H. V.: Conference on Amine Oxidase Inhibitors, New York Academy of Sciences, Nov. 20-22, 1958.

Lakeside Laboratories, Inc. Milwaukee 1, Wisconsin

56559-A

Butazolidin®

(phenylbutazone GEIGY)

tablets · alka capsules

potent · nonhormonal · anti-inflammatory agent

BUTAZOLIDIN tablets or the Alka capsules are **equally effective but individually adaptable in a wide range of arthritic disorders.**

Recent clinical reports continue to justify the selection of Butazolidin for rapid relief of pain, increased mobility, and early resolution of inflammation.

Gouty Arthritis: "...95 per cent of patients experienced a satisfactory response..."[1]

Rheumatoid Arthritis: In "A total of 215 cases... over half, 50.7 per cent showed at least major improvement, with 21.8 per cent showing minor improvement...."[2] **Osteoarthritis:** 301 cases showed "...a total of 44.5 per cent with complete remission or major improvement. Of the remainder, 28.2 per cent showed minor improvement...."[2] **Spondylitis:** All patients "...experienced initial major improvement that was maintained throughout the period of medication."[3] **Painful Shoulder Syndrome:** Response of 70 patients with various forms showed "...8.6 per cent complete remissions, 47.1 per cent major improvement, 20.0 per cent minor improvement...."[2]

References: 1. Graham, W.: Canad. M. A. J. 79:634 (Oct. 15) 1958. 2. Robins, H. M.; Lockie, L. M.; Norcross, B.; Latona, S., and Riordan, D. J.: Am. Pract. Digest Treat. 8:1758, 1957. 3. Kuzell, W. C.; Schaffarzick, R. W.; Naugler, W. E., and Champlin, B. M.: New England J. Med. 256:388, 1957.

Availability BUTAZOLIDIN® (phenylbutazone GEIGY): Red coated tablets of 100 mg. BUTAZOLIDIN® Alka: Capsules containing BUTAZOLIDIN® (phenylbutazone GEIGY), 100 mg.; dried aluminum hydroxide gel, 100 mg.; magnesium trisilicate 150 mg.; homatropine methylbromide, 1.25 mg.

geigy

ARDSLEY, NEW YORK

02959

REPRINT ORDER FORM

THE AMERICAN JOURNAL
OF MEDICINE
11 E. 36th St., New York 16, N. Y.

Please send me the following Seminars reprinted from the AMERICAN JOURNAL OF MEDICINE.

- ☐ CARBOHYDRATE METABOLISM $2.00
- ☐ ALLERGY $2.00
- ☐ DISEASES OF THE PANCREAS $2.00
- ☐ BONE DISEASES $2.00
- ☐ ATHEROSCLEROSIS $2.00
- ☐ LIVER DISEASE $2.00
- ☐ SYMPOSIUM ON RENAL PHYSIOLOGY $4.00

Enclosed is my check

Name_____

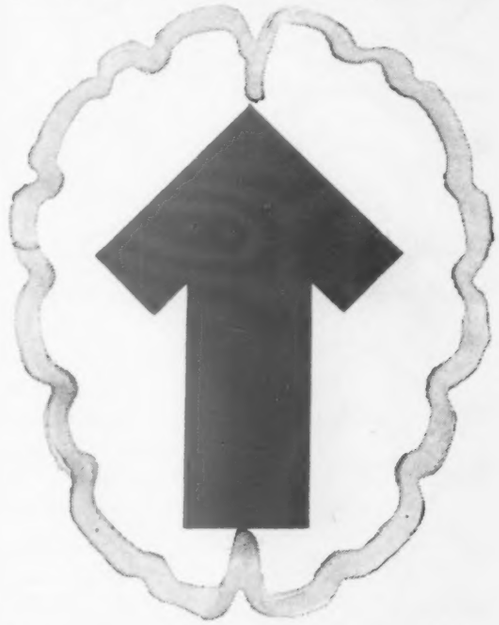
Address_____

City_____ State_____

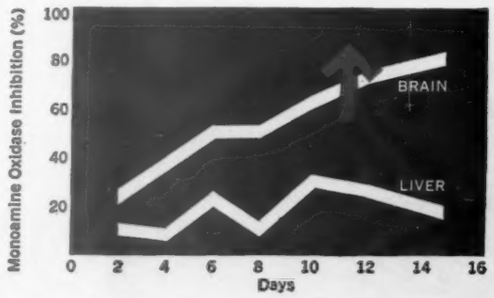
new psychoactive agent

Catron®

β-phenylisopropyl hydrazine supplied as the hydrochloride



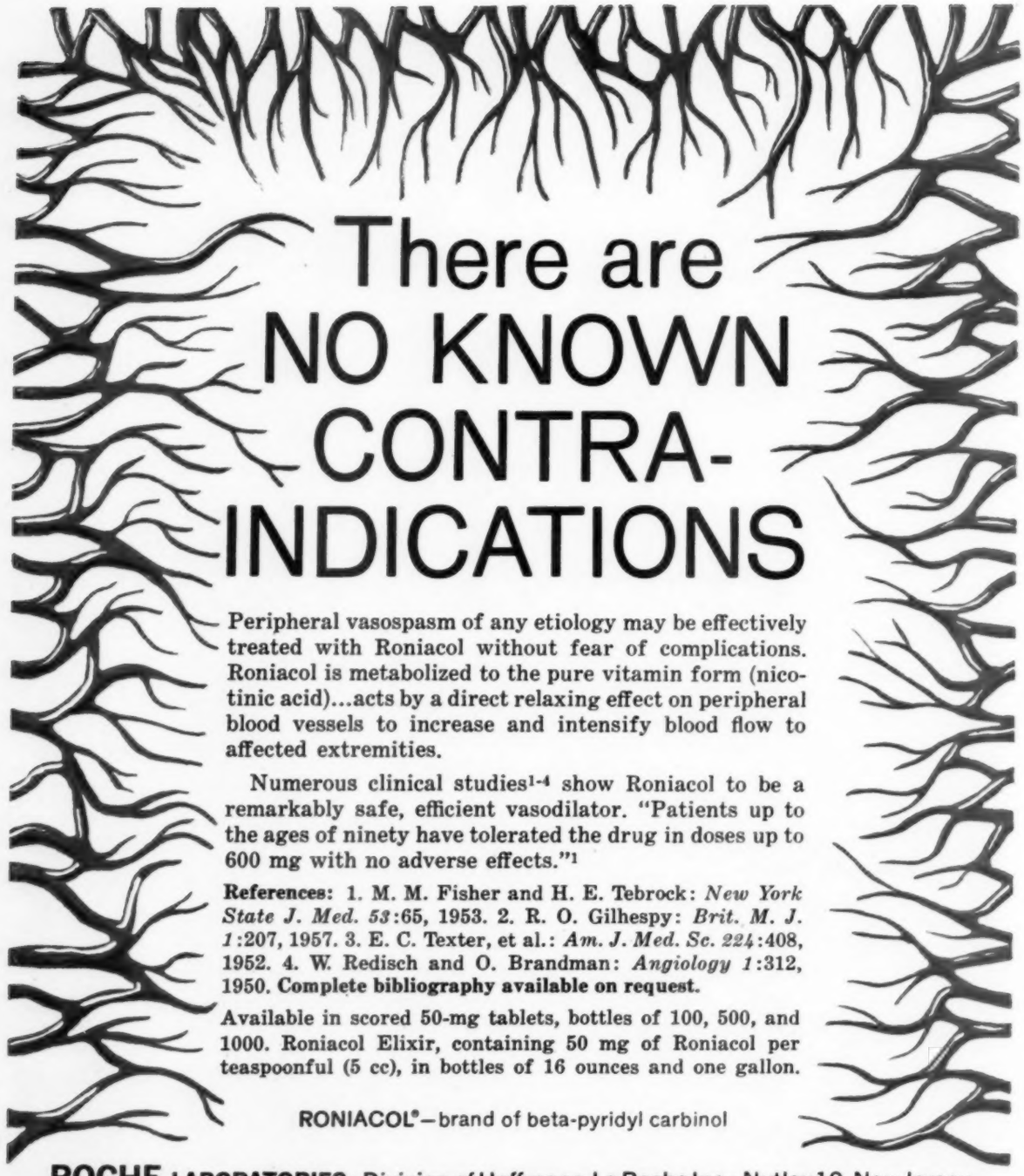
Brightens mood, dispels apathy, melancholy, social withdrawal through selective suppression of monoamine oxidase (MAO) of brain at doses which have little or no effect on liver.



Horita, A.: Report, Mar. 17, 1959

Lakeside Laboratories, Inc. Milwaukee 1, Wisconsin

56559-B



There are NO KNOWN CONTRA-INDICATIONS

Peripheral vasospasm of any etiology may be effectively treated with Roniacol without fear of complications. Roniacol is metabolized to the pure vitamin form (nicotinic acid)...acts by a direct relaxing effect on peripheral blood vessels to increase and intensify blood flow to affected extremities.

Numerous clinical studies[1-4] show Roniacol to be a remarkably safe, efficient vasodilator. "Patients up to the ages of ninety have tolerated the drug in doses up to 600 mg with no adverse effects."[1]

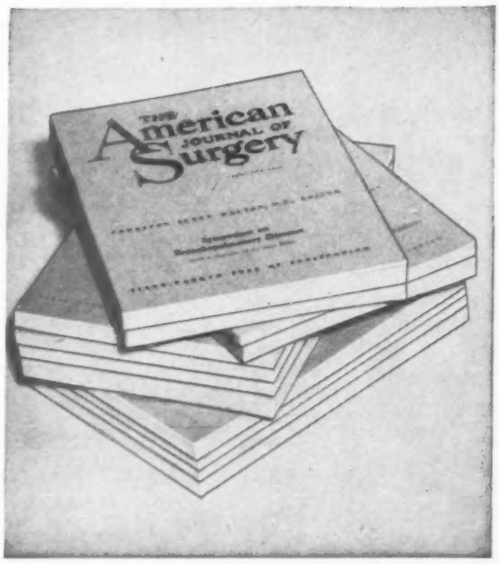
References: 1. M. M. Fisher and H. E. Tebrock: *New York State J. Med. 53*:65, 1953. 2. R. O. Gilhespy: *Brit. M. J. 1*:207, 1957. 3. E. C. Texter, et al.: *Am. J. Med. Sc. 224*:408, 1952. 4. W. Redisch and O. Brandman: *Angiology 1*:312, 1950. **Complete bibliography available on request.**

Available in scored 50-mg tablets, bottles of 100, 500, and 1000. Roniacol Elixir, containing 50 mg of Roniacol per teaspoonful (5 cc), in bottles of 16 ounces and one gallon.

RONIACOL®—brand of beta-pyridyl carbinol

ROCHE LABORATORIES • Division of Hoffmann-La Roche Inc • Nutley 10, New Jersey

RONIACOL for vasodilation



Back Issues Wanted

(MUST BE IN GOOD CONDITION)

THE AMERICAN JOURNAL OF SURGERY

will pay $1.00 per copy for the following issues:

January 1948

April 1955

May 1955

Send Postpaid to

The American Journal of Surgery, Inc.

11 East 36th Street New York 16, N. Y.

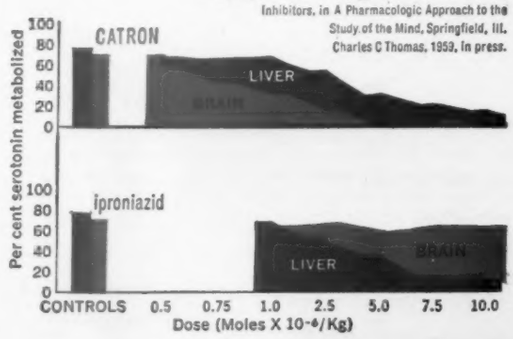
new psychoactive agent

Catron®

β-phenylisopropyl hydrazine supplied as the hydrocnloride

Elevates mood, brightens outlook by raising levels of mood-controlling neurohormones, serotonin and norepinephrine . . . at doses which have little or no effect on the liver.

Horita, A.: The Pharmacology of the Monoamine Oxidase Inhibitors, in A Pharmacologic Approach to the Study of the Mind, Springfield, Ill. Charles C Thomas, 1959, in press.



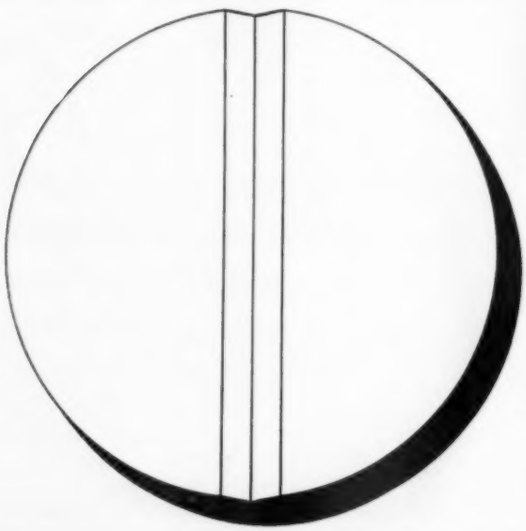
Lakeside Laboratories, Inc. Milwaukee 1, Wisconsin

96559-C

GREATER CONVENIENCE

DOUBLE POTENCY

AT LOW COST TO YOUR PATIENT



Pentids '400'

Squibb 400,000 units Buffered Penicillin G Potassium Tablets

For the treatment of penicillin susceptible infections—ranging from **mild to moderately severe**—due to **hemolytic streptococcus / pneumococcus / staphylococcus / and for the prevention of streptococcal infections where there is a history of rheumatic fever**

Clinical effectiveness confirmed by millions of cases
Specific in many common infections
Daily dosage may be spaced without regard to mealtime
Ease of administration with oral penicillin
Economy for the patient

SQUIBB Squibb Quality—the Priceless Ingredient

new convenient oral tablets

PENTIDS '400,' each scored tablet contains 400,000 units of penicillin G potassium buffered, bottles of 12 and 100. Twice the unitage of Pentids 200,000 units.

also available

PENTIDS, 200,000 units of buffered penicillin G potassium per scored tablet, bottles of 12, 100, and 500.

PENTIDS FOR SYRUP, 200,000 units of penicillin G potassium per teaspoonful (5 cc.), 12 dose bottles.

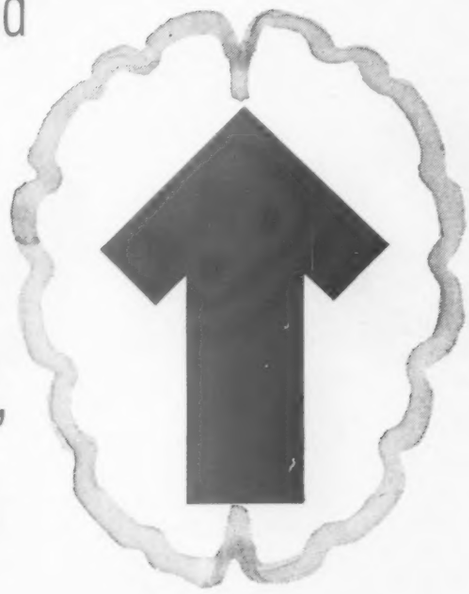
PENTIDS, CAPSULES, 200,000 units of penicillin G potassium per capsule, bottles of 24, 100, and 500.

PENTIDS SOLUBLE TABLETS, 200,000 units of penicillin G potassium per tablet, vials of 12 and bottles of 100.

PENTIDS-SULFAS TABLETS, 200,000 units of penicillin G potassium with 0.5 Gm. triple sulfas per tablet, bottles of 30, 100, and 500.

PENTIDS® IS A SQUIBB TRADEMARK

withdrawn apathetic rejected gloomy
remorseful hopeless listless despairing
forlorn somber defeated
bitter crushed



WHEN THE WORDS MEAN DEPRESSION, THE TREATMENT IS

Catron®

β-phenylisopropyl hydrazine supplied as the hydrochloride

Important new psychoactive agent—acts selectively on the brain to brighten outlook, raise spirits, rebuild self-esteem, revitalize depressed patients.

Lakeside Laboratories, Inc., Milwaukee 1, Wisconsin

56559-D

For detailed information, request Brochure No. 19, CATRON

Important New

Catron®

β-phenylisopropyl hydrazine supplied as the hydrochloride

Lakeside Laboratories, Inc., Milwaukee 1, Wisconsin

How to use this new drug:

CATRON Hydrochloride is a monoamine oxidase (MAO) inhibitor useful in the treatment of depression and of other disorders indicated below. It is recommended for use in carefully selected cases and in those patients who have not responded to the milder drugs.

ADMINISTRATION AND DOSAGE

Dosage of CATRON must be individualized according to each patient's response. The initial daily dose should not exceed 12 mg. and should be reduced as soon as the desired clinical effect is obtained. In severe depressions some clinicians desire rapid results and begin treatment with 24 mg. daily: this dosage should not be continued for more than a few days. A single daily dose in the morning is recommended. A continuous or interrupted schedule may be used, the latter during the maintenance period.

DEPRESSION (Endogenous, Reactive, Postpartum, Involutional and Depression Secondary to Schizophrenic or Neurotic Reaction): initially, 12 mg. once daily for approximately 2 weeks, or less if improvement appears. Dosage is then reduced to 6 mg. daily. As improvement continues, maintenance dosage of 6 mg. every other day or of 3 mg. daily often proves satisfactory. An interrupted dose schedule is recommended for long-term therapy.

ANGINA PECTORIS—3 to 6 mg. daily in most cases. Relief of pain and elevation of mood may be dramatic. Victims of angina pectoris who respond in this manner should be cautioned against overexertion induced by their sense of well-being.

RHEUMATOID ARTHRITIS (Adjunctive Therapy—in severely disabling forms, particularly when accompanied by depression): 9 to 12 mg. daily for 3 days, then 6 mg. daily, reducing further to 3 mg. daily on signs of improvement. If a conventional antiarthritic agent is used, lower doses of each are indicated.

CAUTION

Certain circumstances should be watched carefully when using CATRON.

DRUG POTENTIATION—The list of drugs which CATRON potentiates is not yet complete. CATRON should not be used concomitantly with any other drug unless, (a) it has been ascertained that the two drugs bear no qualitative relationship, or (b) potentiating action is being sought, as may be the case with tranquilizing drugs including reserpine and the phenothiazines, and with the amphetamines, barbiturates and hypotensive agents.

HYPOTENSIVE EFFECT—All normotensive patients receiving CATRON, but especially elderly patients, should be warned about the possibility of orthostatic hypotension during the initial period of higher dosage. In the few instances where this may occur, lowering of the dose will usually permit continuation of therapy.

COLOR VISION—A reversible red-green color defect has been reported in a few patients, chiefly hypertensives, on ex-

Psychoactive Agent

- Brightens mood, diminishes apathy and confusion, curbs symptoms of withdrawal, self-pity, inadequacy, despair.[1,2]
- Acts selectively on brain at doses having little or no effect on liver.[5-7]
- Valuable in depressions associated with chronic diseases such as angina pectoris,[8] severe rheumatoid arthritis.[9]

For detailed information, request Brochure No. 19, CATRON

tended therapy with CATRON. Discontinue the drug if such changes occur.

ANIMALS, NEUROLOGIC SIGNS—In toxicity studies with animals, a neurologic syndrome has been observed characterized by tremors, muscle rigidity and difficulty in locomotion. Although extensive clinical experience has not shown such reactions to be a problem in humans in recommended dosage, should a similar neurologic disturbance occur, the possibility of drug action should be considered.

SIDE EFFECTS—Major side effects requiring cessation of therapy are infrequent. Other side effects—constipation, delay in starting micturition, increased sweating, hyperreflexia, ankle edema, blurring of vision, dryness of the mouth—are usually readily controlled by lowering the dosage. Rash, observed in a few patients, cleared up rapidly upon discontinuing therapy.

WARNING: Pharmacologic studies show that with proper dosage CATRON will inhibit monoamine oxidase in the brain without influencing this enzyme in the liver. This is in contrast to previous inhibitors, which depress monoamine oxidase activity in the liver before affecting this enzyme in the brain.

Although the evidence suggests that serious life-threatening hepatitis seen with other MAO inhibitors should not occur with CATRON in the recommended dosage, it has been reported on rare occasion with dosages in excess of the recommended levels.

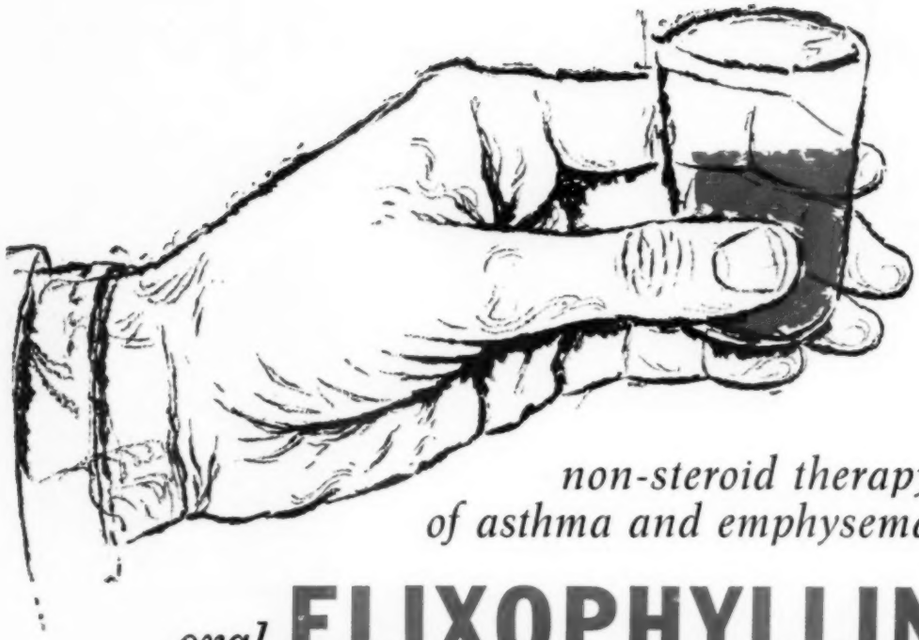
The Following Precautions are Recommended:

1. In all instances daily dose should not exceed 12 mg.
2. Reduce daily dose as soon as response is established, usually in a matter of 1 to 2 weeks.
3. Do not prescribe to a patient more than sixteen 6 mg. tablets or thirty-two 3 mg. tablets of CATRON at one time.
4. Patient should return for observation before additional CATRON is prescribed. For this reason, prescriptions for CATRON should be marked, "not refillable."
5. Perform regular liver function tests.
6. Do not use the drug in patients with a history of viral hepatitis or other liver abnormalities.

CATRON is the original brand of β-phenylisopropyl hydrazine. It is supplied as the hydrochloride in tablets of 3 mg. and 6 mg., bottles of 50.

(1) Agin, H. V.: The Use of JB-516 (CATRON) in Psychiatry, Conference on Amine Oxidase Inhibitors, New York Academy of Sciences, Nov. 20-22, 1958. (2) Bercel, N. A.: A Pharmacologic Approach to the Study of the Mind, Springfield, Ill., Charles C Thomas, 1959, in press. (3) Kinross-Wright, J.: Panel Discussion of Psychic Energizers, *ibid.* (4) Kinross-Wright, J.: Experience with JB-516 (CATRON) and Other Psychochemicals in Clinical Practice, Conference on Amine Oxidase Inhibitors, New York Academy of Sciences, Nov. 20-22, 1958. (5) Horita, A., and Parker, R. G.: Comparison of Monoamine Oxidase Inhibitory Effects of Iproniazid and Its Phenyl Congener, Proc. Soc. Exper. Biol. & Med. 99:617, 1958. (6) Horita, A.: *Beta*-Phenylisopropylhydrazine, A Monoamine Oxidase Inhibitor, Fed. Proc. 17:379, 1958. (7) Horita, A.: The Pharmacology of the Monoamine Oxidase Inhibitors, in A Pharmacologic Approach to the Study of the Mind, Springfield, Ill., Charles C Thomas, 1959, in press. (8) Kennamer, R., and Prinzmetal, M.: Treatment of Angina Pectoris with CATRON (JB-516), Am. J. Cardiol. 3:542, 1959. (9) Scherbel, A. L., and Harrison, J. W.: The Effects of Iproniazid and Some Other Amine Oxidase Inhibitors in Rheumatoid Arthritis, Conference on Amine Oxidase Inhibitors, New York Academy of Sciences, Nov. 20-22, 1958.

56559-E



non-steroid therapy
of asthma and emphysema

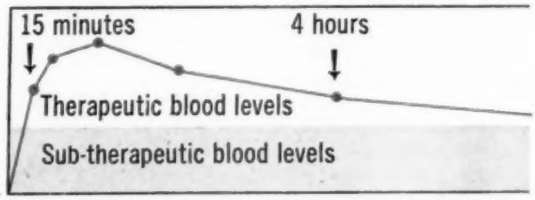
oral ELIXOPHYLLIN

Just as with I.V. aminophylline,* high theophylline blood levels *reached in minutes* – from a single dose.*

After absorption, theophylline is slowly eliminated. Therapeutic blood levels *endure for hours.**

This predictability of blood levels permits quite constant *therapeutic blood levels night and day,* providing relief of wheezing, dyspnea, cough, and protection against acute attacks for most patients.*

DOSAGE: *First two days:*
45 cc. *(three tbsp.)* on arising;
45 cc. *(three tbsp.)* on retiring;
45 cc. *(three tbsp.)* once midway between above doses *(about 3 P.M.)*



After two days of therapy the size of doses should be slightly decreased.
Each tablespoonful contains: theophylline 80 mg., alcohol 3 cc.
Prescription only – bottles of 16 fl. oz.

Sherman Laboratories
Detroit 11, Michigan

**Reprints of these studies on request.*

New ... for the metabolic treatment of

gout

ANTURAN™

(sulfinpyrazone GEIGY)

High Potency Uricosuric Agent

By significantly increasing renal excretion of urate and thus lowering plasma uric acid, the new highly potent uricosuric agent ANTURAN strikes directly at the basic metabolic defect in gout.

Exceptionally high potency...4 to 6 times that of probenecid†...is the outstanding characteristic of ANTURAN. The effectiveness of ANTURAN is retained indefinitely and tolerance to it is good.

Clinically, ANTURAN:

- Prevents formation of new tophi
- Causes gradual absorption of old tophi
- Relieves chronic pain
- Restores joint mobility

ANTURAN is not designed for the treatment of acute attacks for which BUTAZOLIDIN* is recommended. **Detailed Information On Request**

†Yü, T. F.; Burns, J. J., and Gutman, A. B. Arth. & Rheumat. 1:532, 1958.

ANTURAN™ (sulfinpyrazone GEIGY). Scored tablets of 100 mg. in bottles of 100.

*BUTAZOLIDIN® (phenylbutazone GEIGY)

Geigy

Ardsley, New York

INTRODUCING

RUBRAMIN PC

SQUIBB VITAMIN B_{12} U.S.P. INJECTION

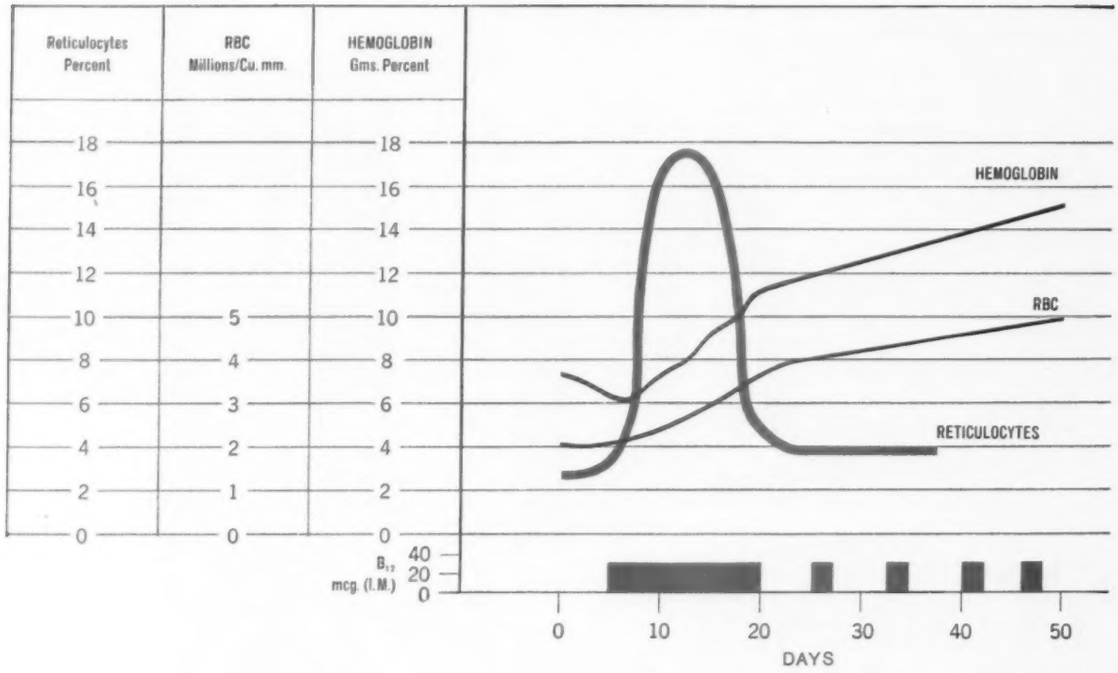
PURE CYANOCOBALAMIN INJECTION – CREATED AND PRODUCED BY SQUIBB – FOR THE MOST EXACTING STANDARDS OF INTRAVENOUS, INTRAMUSCULAR AND SUBCUTANEOUS ADMINISTRATION IN:

- *pernicious anemia*
- *severe nutritional macrocytic anemias*
- *severe nutritional neuropathies*
- *prevention of macrocytic anemia following partial or total gastrectomy*

and for the relief of pain in such conditions as:

trigeminal neuralgia; osteoarthritis; secondary burning paresthesias; herpes zoster; and neuroblastoma in children.

RUBRAMIN PC is highly effective whenever high doses of vitamin B_{12} are required.



TYPICAL HEMATOPOIETIC RESPONSE WHEN RUBRAMIN P C IS GIVEN INTRAMUSCULARLY TO A PATIENT WITH MEGALOBLASTIC ANEMIA *(schematic)*

highly potent and vital to metabolism

Vitamin B_{12} – one of the most potent biological factors known – is vital to basic metabolic functions, to normal formation of red blood cells and other formed elements of the blood, and to the functional integrity of myelinated fibers in the spinal cord and brain, as well as to the healthy condition of gastric and oral mucosa.

therapeutic agent of choice in pernicious anemia

Vitamin B_{12} is the therapeutic agent of choice in pernicious anemia, is effective in certain megaloblastic macrocytic anemias, and contributes to recovery or clinical improvement in a variety of neurological, liver and skin disorders.

non-toxic, remarkably free from side reactions

Despite its high level of activity, vitamin B_{12} is non-toxic and remarkably free from side reactions. It has been well-tolerated even when administered in massive doses.

potency confirmed by precise radioisotope measurement

The Radioisotope Tracer Method is now used routinely as an assay procedure in the production of RUBRAMIN, guaranteeing accurate label potency.

RUBRAMIN P C is now available in potencies for all your parenteral requirements: 30, 50 and 100 mcg. per cc., 10 cc. vials; 1000 mcg. per cc., 1 cc. and 10 cc. vials.

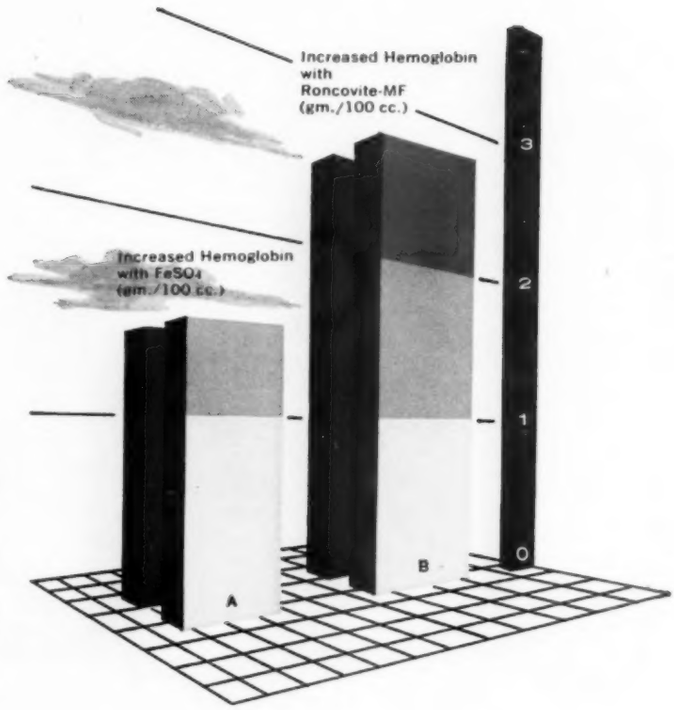
SQUIBB *Squibb Quality – the Priceless Ingredient*

"RUBRAMIN"® IS A SQUIBB TRADEMARK

LEGEND:

(A) Patients receiving ferrous sulfate 200 mg. q.i.d. showed average increase in hemoglobin of 1.5 gm.

(B) Patients receiving Roncovite-MF (15 mg. cobalt chloride and 100 mg. ferrous sulfate) showed average increase in hemoglobin of 2.7 gm.



Improved iron utilization in anemia

RONCOVITE®-mf

Each tablet contains: Cobalt chloride (Cobalt as Co....3.7 mg.)...15 mg. Ferrous sulfate, exsiccated...100 mg.

Improves iron utilization by enhancing the formation of erythropoietin, the erythropoietic hormone

Recent research[1,2] again emphasizes the role of cobalt as the only clinically proved agent which enhances erythropoietin formation.

The acceleration of erythropoiesis with Roncovite therapy provides optimal utilization of iron.

Acting through this physiologic mechanism, Roncovite (cobalt-iron) therapy results in an increased production of red cells and hemoglobin—a better blood picture—a faster, more complete response than iron alone in the common hypochromic anemias—menstrual anemia—anemia of pregnancy—nutritional anemia of infancy—and in anemia due to chronic infection or inflammation.[3,4,5,6,7,8]

(1) Goldwasser, E.; Jacobson, L. O.; Fried, W., and Plzak, L. F.: Blood *13*:55 (Jan.) 1958. (2) Gurney, C. W.; Jacobson, L. O., and Goldwasser, E.: Ann. Int. Med. *49*:363 (Aug.) 1958. (3) Korst, D. R.; Bishop, R. C., and Bethell, F. H.: J. Lab. & Clin. Med. *52*:364 (Sept.) 1958. (4) Ausman, D. C.: Journal-Lancet *76*:290 (Oct.) 1956. (5) Holly, R. G.: Obst. & Gynec. *9*:299 (Mar.) 1957. (6) Holly, R. G.: Clin. Obst. & Gynec. *1*:15 (Mar.) 1958. (7) Diamond, E. F.; Gonzales, F., and Pisani, A.: Illinois M. J. *113*:154 (April) 1958. (8) Hill, J. M.; La Jous, J., and Sebastian, F. J.: Texas J. Med. *51*:686 (Oct.) 1955.

LLOYD BROTHERS, INC. • **CINCINNATI 3, OHIO**

"Deformity in rheumatoid arthritis develops in two stages. The most obvious is joint destruction. But even earlier... muscle spasm...has insidiously started to lead to deformity."[1]

in rheumatoid arthritis...

PARAFON*
with PREDNISOLONE

provides spasmolytic, anti-inflammatory, and analgesic action

dosage: One to two tablets three or four times a day.
supplied: Tablets, scored, buff colored, bottles of 36. Each tablet contains PARAFLEX® Chlorzoxazone† 125 mg.; TYLENOL® Acetaminophen 300 mg.; and Prednisolone 1.0 mg.
precautions: The precautions and contraindications that apply to all steroids should be kept in mind when prescribing PARAFON WITH PREDNISOLONE.

1. Swanson, J. N.: Canad. M. A. J. *79*:638 (Oct. 15) 1958.

McNEIL

McNEIL LABORATORIES, INC • PHILADELPHIA 32, PA.

*Trade-mark †U.S. Patent Pending

265A59

Stop Muscle Spasm

Disipal

Brand of Orphenadrine HCl

in Parkinsonism

An energizing agent against weakness and fatigue... effective as a euphoriant...counteracts sialorrhea and oculogyria...lessens rigidity and tremor...well tolerated...even in presence of glaucoma.

in Low-Back Pain

Effective relief from spasm and pain in painful skeletal muscle disorders due to sprains, strains, herniated intervertebral disc, whiplash injuries, chronic osteoarthritis...No known contraindications.

DOSAGE: Usually 1 tablet (50 mg.) t.i.d.

Riker Northridge* California

*Trademark of Brocades-Stheeman & Pharmacal
U.S. Patent No. 2,567,351. Other patents pending.

CHANGING YOUR ADDRESS?

Please fill out and return the coupon below:

THE AMERICAN JOURNAL OF MEDICINE
Mailing Dept., 11 East 36th Street, New York 16, N. Y.

NAME_____
(please print)

NEW ADDRESS:

Street_____

City_____ Zone_____ State_____

FORMER ADDRESS:

Street_____

City_____ Zone_____ State_____

over and above the rapid relief and improvement of symptoms

Decadron helps restore a "natural" sense of well-being

THE MOST EFFECTIVE OF ALL ANTI-INFLAMMATORY CORTICOSTEROIDS

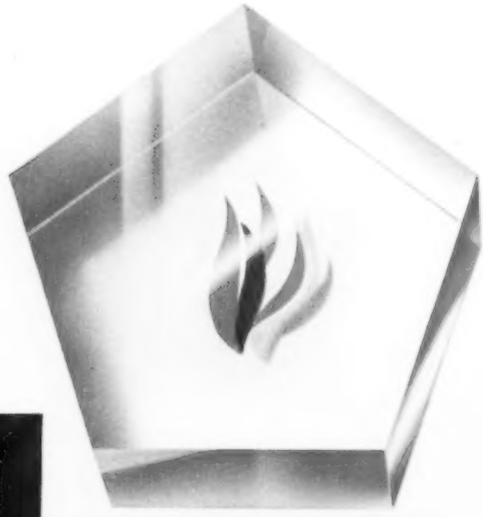
Decadron®

DEXAMETHASONE

treats more patients more effectively

Merck Sharp & Dohme

the crowning achievement of the first corticosteroid decade



Decadron®

DEXAMETHASONE

treats more patients more effectively

Comprehensive and thorough clinical trials show that **DECADRON** on a milligram basis is the most effective of all oral corticosteroids ■ **DECADRON** is virtually free of sodium retention, potassium depletion, hypertension, or edema ■ **DECADRON** is virtually free of diabetogenic effect in therapeutic doses ■ **DECADRON** has not caused any new or unusual reactions ■ **DECADRON** helps restore a "natural" sense of well-being.

INDICATIONS: All allergic and inflammatory disorders amenable to corticosteroid therapy. **CONTRAINDICATIONS:** Herpes simplex of the eye is an absolute contraindication to corticosteroid therapy. DECADRON should be administered with the same precautions observed with other corticosteroid therapy. **DOSAGE AND ADMINISTRATION:** Transfer of patients from other corticosteroids to DECADRON may usually be accomplished on the basis of the following milligram equivalence:

one 0.75 mg. tablet of **Decadron** (dexamethasone) replaces:

↓ One 4 mg. tablet of	↓ One 5 mg. tablet of	↓ One 20 mg. tablet of	↓ One 25 mg. tablet of
methylprednisolone or triamcinolone	prednisolone or prednisone	hydrocortisone	cortisone

SUPPLIED: As 0.75 mg. scored pentagon-shaped tablets. Also as 0.5 mg. tablets, to provide maximal individualized flexibility of dosage adjustment, since many patients achieve adequate control even on lower dosage.

Detailed literature is available on request.
DECADRON is a trademark of Merck & Co., Inc.

MSD Merck Sharp & Dohme
Division of Merck & Co., Inc., Philadelphia 1, Pa.

IMPROVING ON NATURE

A luxurious gift of nature—the wheat field is of more value to man because he has modified it to meet his specific requirements. Such an improvement on nature is also found in the treatment of hypothyroidism. Here the response to Proloid provides a dramatic example of man's ability to improve what nature has provided.

Proloid not only restores the patient to a euthyroid state—it does it safely and consistently. The only purified but complete thyroglobulin, it never varies in potency from prescription to prescription—the result of an exclusive double assay.

Prescribe Proloid; 3 grains is the average dosage for the mild hypothyroid patient.

PROLOID®

dependable
safe
economical

WARNER
CHILCOTT
MORRIS PLAINS, N.J.

NEW A SENTRY FOR THE G.I. TRACT

protects against
hypersecretion • hypermotility
hyperirritability • hyperemotivity

ENA

anticholinergic / antispasmodic / tranquilizer

A remarkably long-acting anticholinergic. Only one 10 mg. dose of new long-acting oxyphencyclimine controls hypersecretion and spasm[3] for 12 hours or more. In the most recent study at Cook County Hospital, investigators were impressed with its antisecretory effect, leading to prolonged periods of achlorhydria.[6] 51 out of 57 patients with various G.I. disorders were relieved of symptoms on only 2 daily doses.

Plus ATARAX—the antisecretory tranquilizer. Not only does ATARAX modify tension—its added antisecretory action[4,7-9] augments the efficacy of oxyphencyclimine. The combination, ENARAX, freed 100 out of 103 patients of G.I. symptoms.[2] Improvement was especially notable in cases of peptic ulcer, where the emotional factor figures so prominently.

"Side reactions were uncommon...."[2] Selective postganglionic action on the G.I. tract minimizes side effects. Mouth dryness—the most common reaction—seldom reaches troublesome proportions.

Each ENARAX tablet contains: Oxyphencyclimine HCl, 10 mg.; Hydroxyzine HCl (ATARAX®), 25 mg.

Dosage: One-half to one tablet twice daily—preferably in the morning and before retiring. The maintenance dose should be adjusted according to therapeutic response. Use with caution in patients with prostatic hypertrophy or glaucoma.

Supplied: In bottles of 60 black-and-white scored tablets.

SUMMARY OF CASES

Clinical Diagnosis	*Oxyphencyclimine[1,2,3,4]	†ENARAX[2,5]
Peptic ulcer	440	48
Gastritis	16	17
Gastroenteritis	—	55
Colitis	37	—
Duodenitis	6	3
Functional bowel syndrome	14	—
Hiatus hernia (symptomatic)	16	1
Pylorospasm or cardiospasm	11	2
Irritable bowel	11	—
Biliary tract dysfunctions	11	1
Miscellaneous	7	29
Total number of patients	569	156
Clinical Results *Excellent*	445	150
Fair	56	—
Failure	68	6

* **Oxyphencyclimine alone**—clinically effective in 87% after a year's testing.

† **ENARAX** (oxyphencyclimine plus ATARAX)—all successful cases in "excellent" category.

RAX®

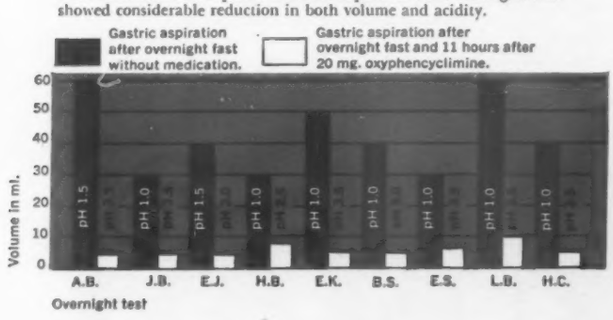
A SENTRY FOR THE G.I. TRACT

one tablet at breakfast
one tablet at bedtime
for *full-time* relief

(oxyphencyclimine plus ATARAX®)

ACID REDUCTION AFTER OXYPHENCYCLIMINE THERAPY

Tests conducted in 9 representative ulcer patients after overnight fasts showed considerable reduction in both volume and acidity.



References: 1. Winaelstein, A.: Am. J. Gastroenterol., in press. 2. Leming, B. H., Jr.: Clin. Med. 6:423 (March) 1959. 3. McHardy, G., et al.: Paper presented at Postgraduate Course in Gastroenterology, University of California School of Medicine, San Francisco, Calif., January 27, 1958. 4. Struh, I. H., and Carballo, A.: To be published. 5. Data in Roerig Medical Department files. 6. Steigmann, F.: To be published. 7. Schuller, E.: Gaz. des Hôpitaux *10*:391 (Apr. 10) 1957. 8. Farah, L.: Internat. Rec. Med. *169*:379 (June) 1956. 9. Harrisson, J. W. E., et al.: Paper presented at the 4th Pan-American Congress of Pharmacy and Biochemistry, Washington, D. C., November 3-9, 1957.

ROERIG Rx

New York 17, N. Y.
Division, Chas. Pfizer & Co., Inc.
Science for the World's Well-Being

ROCHE LABORATORIES IS PRIVILEGED TO ANNOUNCE A NEW DEVELOPMENT TO STOP AS WELL AS PREVENT VOMITING AND NAUSEA

Tigan

The first specific antiemetic/antinauseant·entity

TIGAN IS NOT A CONVERTED ANTIHISTAMINE, NOT A CONVERTED TRANQUILIZER, NOT A CONVERTED SEDATIVE, NOT A COMBINATION

1

Chemically
different as well as new —
a specific antiemetic entity.[1]

2

Pharmacologically
different as well as new —
no demonstrable effects
other than antiemesis.[2]

3

Therapeutically
different as well as new —
stops *active* vomiting in
addition to prophylactically
preventing nausea and
emesis.[1,3-5]

4

Clinically
different as well as new —
effective against vomiting
and nausea in the widest
range of common and special
situations, such as
pregnancy, travel sickness,
gastrointestinal disorders,
uremia, carcinomatosis,
drug poisoning,
radiation sickness,
postoperative states.[1,3,4-6]

5

Practically
different as well as new —
patients may drive,
fly and work in hazardous
situations, even when
previously interdicted
with other agents.[1,2,4-6]

Controlled clinical investigations encompassing 3,000 patients have been completed to date.

No special precautions—
No known contraindications

Tigan affords such antiemetic efficacy, safety and pharmacologic precision that virtually all of the special precautions that have complicated older therapies are obviated. The singular absence of side effects makes it possible to use Tigan even in the presence of common contraindications of older antiemetics.[1-9]

Dosage: **The recommended adult dosage is one or two capsules four times a day.**

Available: **Capsules — 100 mg, blue-and-white, bottles of 100 and 500.**

References: 1. Reports on file, Roche Laboratories. 2. W. Schallek, G. A. Heise, E. F. Keith and R. E. Bagdon, *J. Pharmacol. & Exper. Therap.*, in press. 3. I. Roseff, W. B. Abrams, J. Kaufman, L. Goldman and A. Bernstein, *J. Newark Beth Israel Hosp.*, *9*:189, 1958. 4. W. B. Abrams, to be published. 5. O. Brandman, to be published. 6. Personal communications. 7. P. K. Conner, Jr., S. Kinard, W. Fraser, H. Bennett and J. H. Moyer, Scientific Exhibit, A.M.A. Clinical Meeting, Seattle, Nov. 27-30, 1956. 8. *New and Nonofficial Drugs*, Philadelphia, J. B. Lippincott Co., 1959, p. 362. 9. J. H. Moyer, in *Drugs of Choice 1958-1959*, St. Louis, The C. V. Mosby Co., 1958, p. 336.

TIGAN™—brand of trimethobenzamide ROCHE®

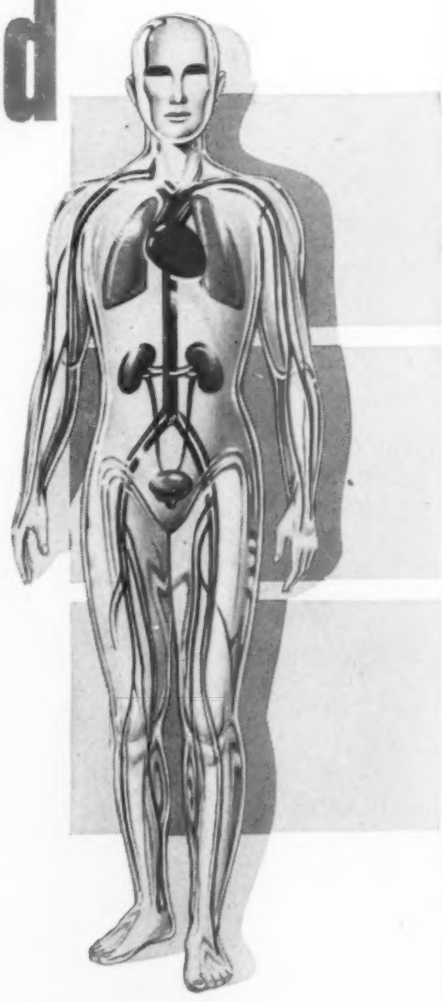
ROCHE LABORATORIES
Division of Hoffmann-La Roche Inc.
Nutley 10, N. J.

NEW

HYDRODIURIL™

(HYDROCHLOROTHIAZIDE)

simplifies* and improves any regimen for hypertension



*it's as easy as 1, 2, 3 to use

HYDRODIURIL™

(HYDROCHLOROTHIAZIDE)

1 Initiate therapy with HYDRODIURIL: one 25 mg. tablet or one 50 mg. tablet once or twice a day. HYDRODIURIL by itself often causes an adequate drop in blood pressure over a period of two to three weeks. This may be all the therapy some patients require.

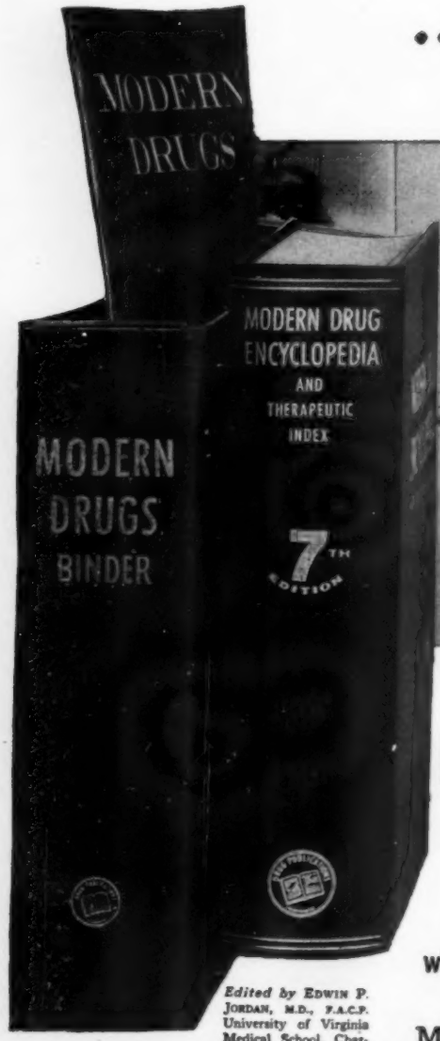
2 Add or adjust other agents as required: HYDRODIURIL enhances the activity of all commonly-used antihypertensive agents; thus, the dosage of other medication (rauwolfia, reserpine, hydralazine, veratrum) should be initiated or adjusted as indicated by patient condition. If a ganglion-blocking agent is contemplated or being used, usual dosage must be reduced by 50 per cent.

3 Adjust dosage of all medication: the patient must be frequently observed and careful adjustment of all agents should be made to establish optimal maintenance dosage.

Supplied: 25 mg. and 50 mg. scored tablets HYDRODIURIL (Hydrochlorothiazide) bottles of 100 and 1,000.
Additional literature for the physician is available on request.

HYDRODIURIL is a trademark of Merck & Co., Inc. Trademarks outside the U. S.: DICHLOTRIDE, DICLOTRIDE, HYDROSALURIC.

MSD MERCK SHARP & DOHME, Division of Merck & Co., Inc., Philadelphia 1, Pa.



Edited by EDWIN P. JORDAN, M.D., F.A.C.P. University of Virginia Medical School, Charlottesville, Virginia.

..."my indispensable source for new drug descriptions"

7th Edition

MODERN DRUG ENCYCLOPEDIA

AND THERAPEUTIC INDEX

with FREE 3-YEAR bi-monthly supplement service, MODERN DRUGS

More than 70% of the prescriptions written today call for new drugs introduced within the past 3 years. It's imperative that your drug reference be complete, dependable, current and up-to-date. Here is your authority on PRESCRIPTION DRUGS and the *new* NARCOTIC CLASSIFICATIONS—your up-to-the-minute source for latest composition or description, action, use, supply, dosage, caution and administration data on more than 4,000 drugs.

★ INDEXED to save you time. Therapeutic, Drug, Manufacturer's and new Generic Name Indices plus self-pronouncing drug listings.

★ COMPLETE, authoritative, continuing service for 3 years—New 7th Edition plus 18 bi-monthly MODERN DRUGS Supplements—all for $17.50.

★ ATTRACTIVELY BOUND in durable red cover stock. Approx. 1500 pages. Size 6" x 9¼" x 2¼".

ORDER THIS 3-YEAR SERVICE TODAY

DRUG PUBLICATIONS, INC. M-9/59*
11 East 36th Street, New York 16, New York

☐ Please send me the 7th Edition MODERN DRUG ENCYCLOPEDIA and Therapeutic Index, plus bi-monthly MODERN DRUGS Supplements for 3 years—all for $17.50*.
☐ Send along Binder for MODERN DRUGS Supplements—$3.00
☐ Remittance Enclosed ☐ Bill me later

Name_____

Address_____

City_____ Zone_____ State_____

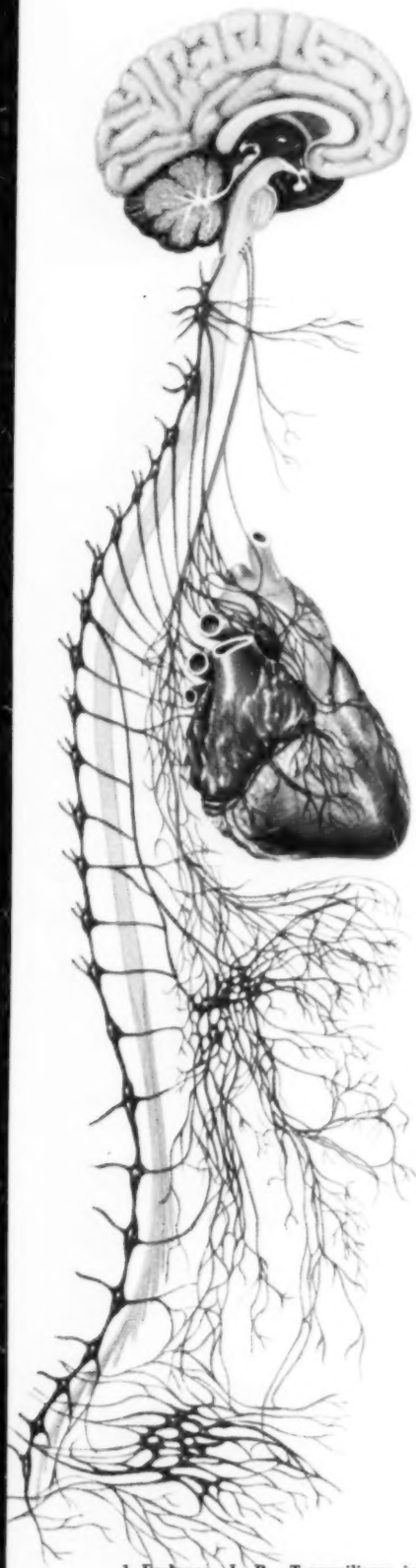
*$17.50 in U.S.A., Foreign, $21.00

Sleepy . . . sleepier . . . asleep! Placidyl's light touch does the trick. Brief. Effective.
Not a barbiturate. Your patients sleep soundly, wake next morning refreshed. Put Placidyl to work in your own practice, soon.

ABBOTT

Placidyl® nudges your patient to sleep

(Ethchlorvynol, Abbott)



and the evidence mounts

In two recent studies, involving 179 mixed anxiety and hypertensive patients—Harmonyl produced far less lethargy and listlessness than Reserpine—and yet with comparable potency and effectiveness. Below, two charts taken from these reports dramatically illustrate the exceptionally low incidence of side reactions with Harmonyl.

RESULTS OF "DOUBLE-BLIND" STUDY OF 99 MIXED ANXIETY AND TENSION PATIENTS[1]

Side Effects	Tablet A Deserpidine 43 patients	Tablet C Placebo 24 patients	Tablet C Reserpine 27 patients
DIZZINESS	0 (0%)	3 (12%)	4 (15%)
DRYNESS OF MOUTH	3 (7%)	1 (4%)	6 (22%)
BIZARRE DREAMS	0 (0%)	2 (8%)	7 (26%)
LISTLESSNESS	1 (2%)	4 (17%)	9 (33%)
DETACHMENT (Diminished awareness)	0 (0%)	0 (0%)	2 (7%)
ANOREXIA	1 (2%)	3 (12%)	4 (15%)
WEAKNESS, TIREDNESS, NO PEP	0 (0%)	8 (33%)	16 (59%)
DAYTIME SLEEPINESS	1 (2%)	4 (17%)	19 (70%)
HEADACHE	0 (0%)	18 (75%)	4 (15%)
NAUSEA	0 (0%)	2 (8%)	3 (11%)
ABDOMINAL CRAMPS	1 (2%)	4 (17%)	5 (18%)
RASH	0 (0%)	0 (0%)	0 (0%)
NASAL STUFFINESS	1 (2%)	0 (0%)	4 (15%)
LOOSE STOOLS	0 (0%)	1 (4%)	3 (11%)

Percentages supplied by Abbott Laboratories.

Author's Comments: "With deserpidine there was less abrupt hypotensive action on blood pressure than with reserpine, and less fatigue or sleepiness during the day."

COMPARISON OF SIDE EFFECTS IN 80 HYPERTENSIVES TREATED WITH VARIOUS FORMS OF RAUWOLFIA[2]

Side Effects	Reserpine	Alseroxylon	Deserpidine	Rescinnamine
LETHARGY	11	10	1	1
NASAL OBSTRUCTION	10	8	8	2
DREAMS	8	7	3	1
ACHING	8	7	3	0
DEPRESSION	3	3	0	1
DIARRHEA	2	3	1	0

Author's Comments: "Deserpidine when given in the morning, showed a definitely lower incidence of lethargy, and depression was not encountered in any patient."

1. Frohman, I. P., Tranquilizers in General Practice and Clinical Evaluation of Deserpidine, an Alkaloid of Rauwolfia Canescens, M. Ann. District of Columbia, 27:641, December, 1958.

2. Winsor, T., Comparative Effects of Various Rauwolfia Alkaloids in Hypertension, Diseases of the Chest, April, 1959.

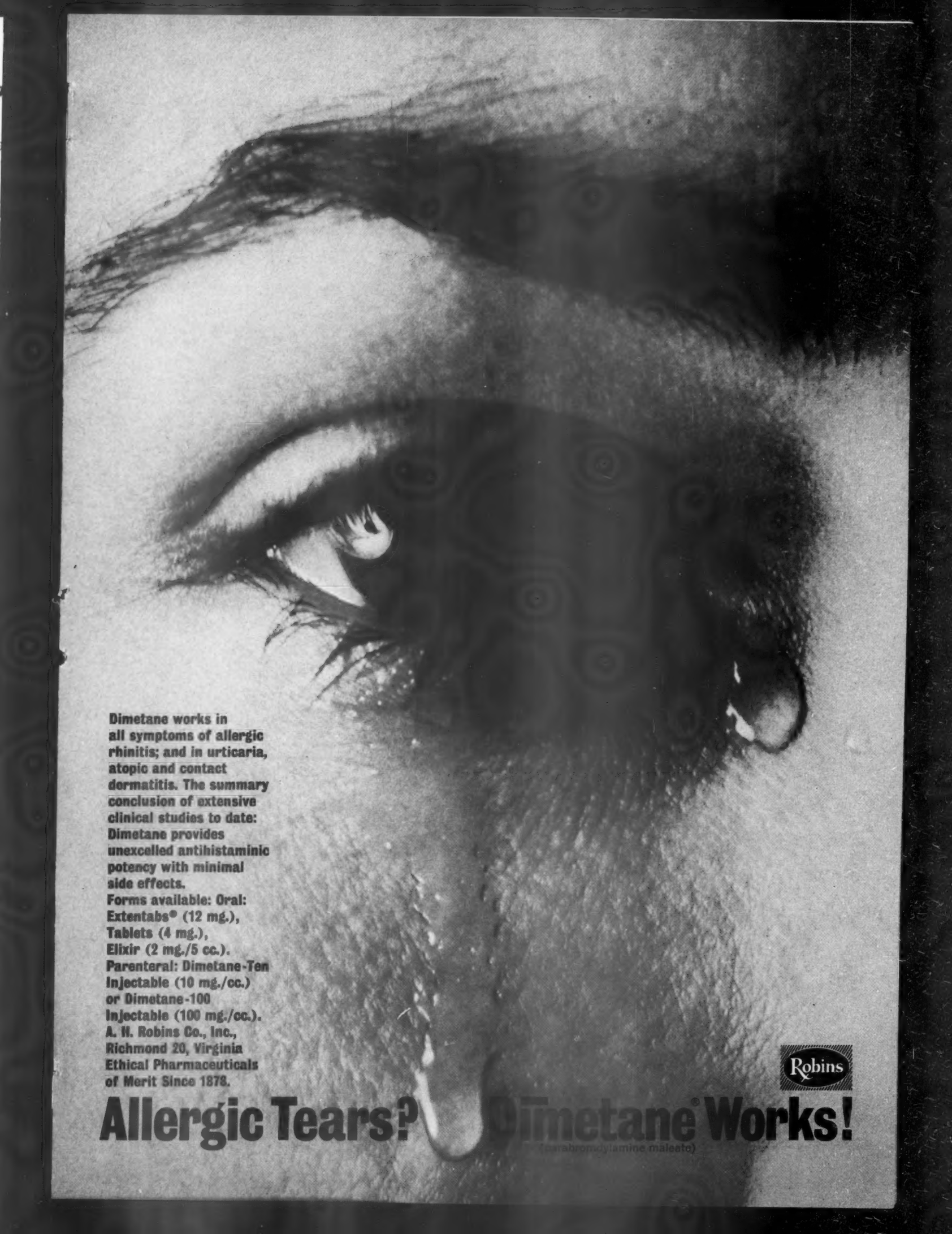
908050

Harmonyl®

(Deserpidine, Abbott)

for your next working hypertensive

ABBOTT


Dimetane works in all symptoms of allergic rhinitis; and in urticaria, atopic and contact dermatitis. The summary conclusion of extensive clinical studies to date: Dimetane provides unexcelled antihistaminic potency with minimal side effects.
Forms available: Oral: Extentabs® (12 mg.), Tablets (4 mg.), Elixir (2 mg./5 cc.). Parenteral: Dimetane-Ten Injectable (10 mg./cc.) or Dimetane-100 Injectable (100 mg./cc.).
A. H. Robins Co., Inc., Richmond 20, Virginia
Ethical Pharmaceuticals of Merit Since 1878.
Robins
Allergic Tears?
Dimetane® Works!
(brompheniramine maleate)

in epilepsy

PREREQUISITE FOR EMOTIONAL ADJUSTMENT: THERAPY

"The most effective form of psychotherapy is to demonstrate to the patient that his seizures can be adequately controlled by the use of anticonvulsant medication."[1]

REQUISITE FOR THERAPY:

THE PARKE-DAVIS FAMILY OF ANTICONVULSANTS

effective anticonvulsants for most clinical needs

bibliography: (1) Carter, S. M.: *M. Clin. North America:* **315** (March) 1953. (2) Chao, D. H.: *Ibid.*, p. 465. (3) Goodman, L. S., & Gilman, A.: The Pharmacological Basis of Therapeutics, ed. 2, New York, MacMillan Company, 1955, p. 187. (4) Davidson, D. T., Jr., in Conn, H. F.: Current Therapy 1958, Philadelphia, W. B. Saunders Company, 1958, p. 568. (5) Zimmerman, F. T.: *New York J. Med.* **55**:2338, 1955. (6) French, E. G.; Rey-Bellet, J., & Lennox, W. G.: *New England J. Med.* **258**:892 (May 1) 1958.

FOR CONTROL OF GRAND MAL AND PSYCHOMOTOR SEIZURES

DILANTIN® KAPSEALS®

"...DILANTIN Sodium is the most useful nonsedative anticonvulsant."[2]

"Coincident with the decrease in seizures there occurs improvement in intellectual performance. Salutary effects of the drug on personality, memory, mood, cooperativeness, emotional stability, amenability to discipline . . . are also observed, sometimes independently of seizure control."[3]

The drug of choice for control of grand mal and of psychomotor seizures, DILANTIN Sodium (diphenylhydantoin sodium, Parke-Davis) is supplied in many forms including Kapseals of 0.03 Gm. and of 0.1 Gm., in bottles of 100 and 1,000.

PHELANTIN® KAPSEALS

"When it has been demonstrated that the combination of Dilantin and phenobarbital is helpful in a patient and that these drugs are well tolerated, the use of a combination capsule, PHELANTIN, is often a great morale builder because it enables the physician to reduce the total number of pills or capsules the patient is required to take. It is a cheaper form of prescription and it also prevents the patient from manipulating the dosage of his drugs."[4]

PHELANTIN Kapseals (Dilantin 100 mg., phenobarbital 30 mg., desoxyephedrine hydrochloride 2.5 mg.), bottles of 100.

FOR THE PETIT MAL TRIAD

MILONTIN® KAPSEALS • SUSPENSION

After five years of study, using MILONTIN in a series of 200 patients with petit mal epilepsy, one investigator reports: "Results confirm our previously published data on a smaller number of cases and show that MILONTIN is an effective agent for the treatment of petit mal epilepsy . . . relatively free from untoward side effects."[5]

MILONTIN Kapseals (phensuximide, Parke-Davis) 0.5 Gm., bottles of 100 and 1,000. Suspension, 250 mg. per 4 cc., 16-ounce bottles.

CELONTIN® KAPSEALS

In a recent study, 76 patients were treated with CELONTIN for periods up to two years. Included in this group were 34 patients with psychomotor seizures, 29 with petit mal, and 13 with other types. Forty per cent had marked benefit with CELONTIN (less than half their previous number of seizures), and all but 35 per cent experienced some degree of improvement. Marked benefit was obtained in 55 per cent of patients with petit mal and in 33 per cent of those having psychomotor seizures.[6]

CELONTIN Kapseals (methsuximide, Parke-Davis) 0.3 Gm., bottles of 100.

PARKE, DAVIS & COMPANY
DETROIT 32, MICHIGAN

MEDICAMENTA VERA

72559

greater antihypertensive effect...fewer side effects

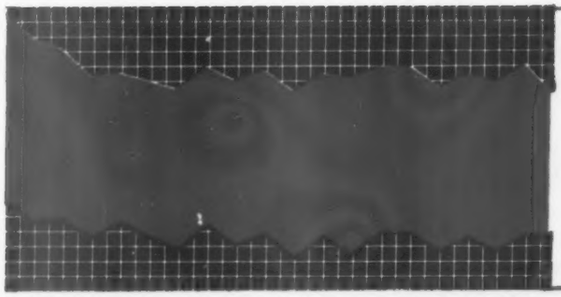
HYDROPRES*

HYDRODIURIL® HYDROCHLOROTHIAZIDE antihypertensive

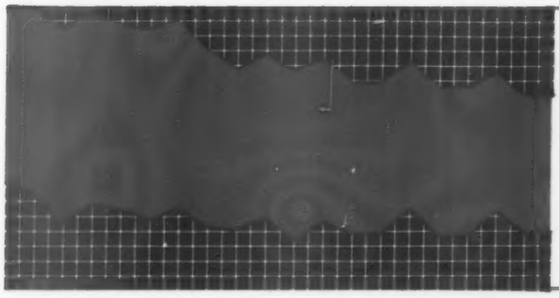
WITH

RESERPINE antihypertensive-tranquilizer

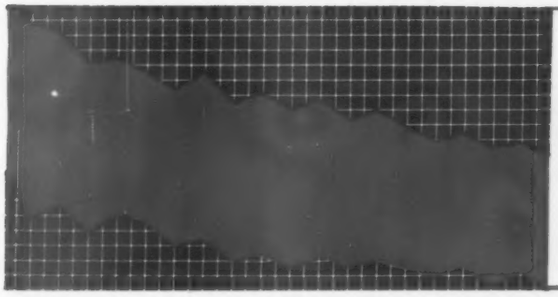
For complete information write Professional Services, Dept. H, Merck Sharp & Dohme, West Point, Pa.



HYDRODIURIL alone



RESERPINE alone



HYDROPRES
much more effective
than either of its
components alone

- Effective by itself in a majority of patients. Provides smooth, more trouble-free management of hypertension.
- Since HYDRODIURIL and reserpine potentiate each other, the required dosage of each is lower when given together as HYDROPRES than when either is given alone.
- HYDROPRES provides the needed and valuable tranquilizing effect of reserpine. Lower dosage may reduce such side effects of reserpine as excessive sedation and depression.
- Arrest or reversal of organic changes of hypertension may occur.
- Headache, dizziness, palpitations and tachycardia are usually promptly relieved. Anginal pain may be reduced in incidence and severity.
- With HYDROPRES, dietary salt may be liberalized.
- Convenient, controlled dosage.

HYDROPRES-25

25 mg. HYDRODIURIL, 0.125 mg. reserpine.
One tablet one to four times a day.

HYDROPRES-50

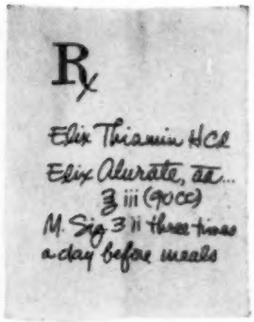
50 mg. HYDRODIURIL, 0.125 mg. reserpine.
One tablet one or two times a day.

If the patient is receiving ganglion blocking drugs or hydralazine, their dosage must be cut in half when HYDROPRES is added.

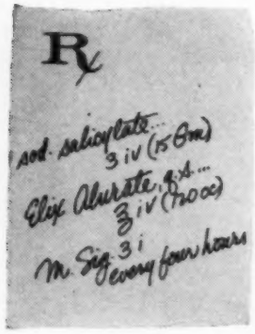
MSD **MERCK SHARP & DOHME,** DIVISION OF MERCK & CO., INC., PHILADELPHIA 1, PA.

*HYDRODIURIL AND HYDROPRES ARE TRADEMARKS OF MERCK & CO., INC.

Whenever your Rx requires a sedative component...



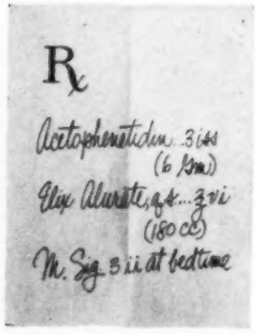
Rx FOR NERVOUS ANOREXIA



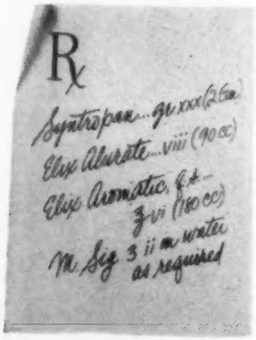
Rx FOR NEURITIC PAIN

widely compatible **Alurate** sedative-hypnotic

Combines prompt action, broad margin of safety and virtual freedom from after-effects in a host of common conditions



Rx FOR INSOMNIA DUE TO PAIN



Rx FOR SPASTIC DYSMENORRHEA

To avoid identification or abuse of the barbiturate component, Alurate is available as Elixir Alurate (cherry-red) and Elixir Alurate Verdum (emerald-green).

ALURATE® brand of aprobarbital.
ROCHE®

Roche Laboratories *Division of Hoffmann-La Roche Inc.*
Nutley 10, New Jersey

AL-20

Index to Advertisers

August, 1959

Abbott Laboratories . . . . . *Insert Facing Page* 126
Ames Company, Inc. 2, 50
Armour Pharmaceutical Company 20
Ayerst Laboratories 11, 15

Burroughs Wellcome & Co., Inc. 26

Ciba Pharmaceutical Products, Inc. . . . . 54–55, 75, 92–93, *Fourth Cover*
Corn Products Company 85

Eaton Laboratories 42–43, 70, 88–89
Endo Laboratories 10

Geigy Company 76–77, 100, 102, 111

Hyland Laboratories 14

Lakeside Laboratories, Inc. 53, 101, 103, 105, 107–108–109
Lederle Laboratories Division, American Cyanamid Company 16–17, 72–73
Thos. Leeming & Co., Inc. 98
Eli Lilly and Company 68
Lloyd Brothers, Inc. 114

The S. E. Massengill Company . . . . . *Insert Facing Page* 50
McNeil Laboratories, Inc. 32, 41, 115
Mead Johnson 49
Merck Sharp & Dohme . . . . . 65, *Insert Facing Page* 116, 124–125, 132–133

Nuclear-Chicago Corp. 40

Organon, Inc. 6
Ortho Pharmaceutical Corp. 19

Parke, Davis & Company 44–45, 130–131
Pfizer Laboratories, Division of Chas. Pfizer & Co., Inc. . . . 12, 24, 35, 56–57, 60–61, 78–79
Pitman-Moore Company . . . . . *Insert Facing Page* 32

Riker Laboratories, Inc. . . . . 116, *Third Cover*
A. H. Robins Co., Inc. 86–87, 129
Roche Laboratories, Div. of Hoffmann-LaRoche Inc. . . . 36, 58, 62–63, 104, 122–123, 134
J. B. Roerig & Co. 59, 90–91, 120–121
William H. Rorer, Inc. 97

Sandoz Pharmaceuticals, Division of Sandoz, Inc. 66–67
Schenlabs Pharmaceuticals, Inc. 13
Schering Corporation 31, 39
G. D. Searle & Co. 69
Sherman Laboratories 110
Smith Kline & French Laboratories 23, 25, 27
E. R. Squibb & Sons, Division of Mathieson Chemical Corp. . . . 8, 22, 71, 99, 106, 112–113
Sunkist Growers 37

The Upjohn Company 38, 95

Wallace Laboratories 48, 96, 136
Warner-Chilcott Laboratories 1, 119
White Laboratories, Inc. 46–47
Winthrop Laboratories . . . . . 4, *Insert Facing Page* 80
Wyeth Laboratories 18, 21, 29, 30, 74, 80
Wynn Pharmacal Corporation 28

THE HEART DISEASE PATIENT NEEDS RELIEF FROM EMOTIONAL STRESS

ANXIETY INTENSIFIES the physical disorder in heart disease. "The prognosis depends largely on the ability of the physician to control the anxiety factor, as well as the somatic disease."

(Friedlander, H. S.: The role of ataraxics in cardiology. Am. J. Cardiol. 1:395, March 1958.)

TRANQUILIZATION WITH MILTOWN enhances recovery from acute cardiac episodes and makes patients more amenable to necessary limitations of activities.

(Waldman, S. and Pelner, L.: Management of anxiety associated with heart disease. Am. Pract. & Digest Treat. 8:1075, July 1957.)

Miltown®

meprobamate (Wallace)

Available in 400 mg. scored and 200 mg. sugar-coated tablets. Also available as MEPROSPAN* (200 mg. meprobamate *continuous release* capsules). In combination with a nitrate, for angina pectoris: MILTRATE*—(Miltown 200 mg. + PETN 10 mg.). *TRADE-MARK CM-772G

Miltown causes no adverse effects on heart rate, blood pressure, respiration or other autonomic functions.

WALLACE LABORATORIES, *New Brunswick, N. J.*

For Emotionally Disturbed Children

- **whose intelligence is masked by behavior problems...**
- **who are unable to concentrate...**
- **whose attention span is too short...**

"Children came to act in more socially accepted patterns...learning in school improved...within a single grading period (usually 6 weeks)...in many the ease and speed of reading was greatly increased. The ability to do arithmetic improved remarkably in some of the children."

Oettinger, L., Jr.: The Use of Deanol (Deaner) in the Treatment of Disorders of Behavior in Children, J. Pediat. *53*:671 (Dec.) 1958.

"Effective in increasing alertness, awareness, spontaneity, energy, and ability to concentrate."

Toll, N.: Deaner: An Adjunct for Treatment of Schizoid and Schizophrenic Patients, Am. J. Psychiat. *115*:336 (Oct.) 1958.

Effects of Deaner, after coming on gradually, are prolonged...virtually no side effects.

Deaner®

Dosage for children: Initially ½ to 1 tablet in the morning. Maintenance dose ½ to 3 tablets. Full benefits may require two weeks or more of therapy. • Supplied in scored tablets containing 25 mg. of 2-dimethylaminoethanol as the *p*-acetamidobenzoic acid salt. Available in bottles of 100.

Riker

Northridge, California

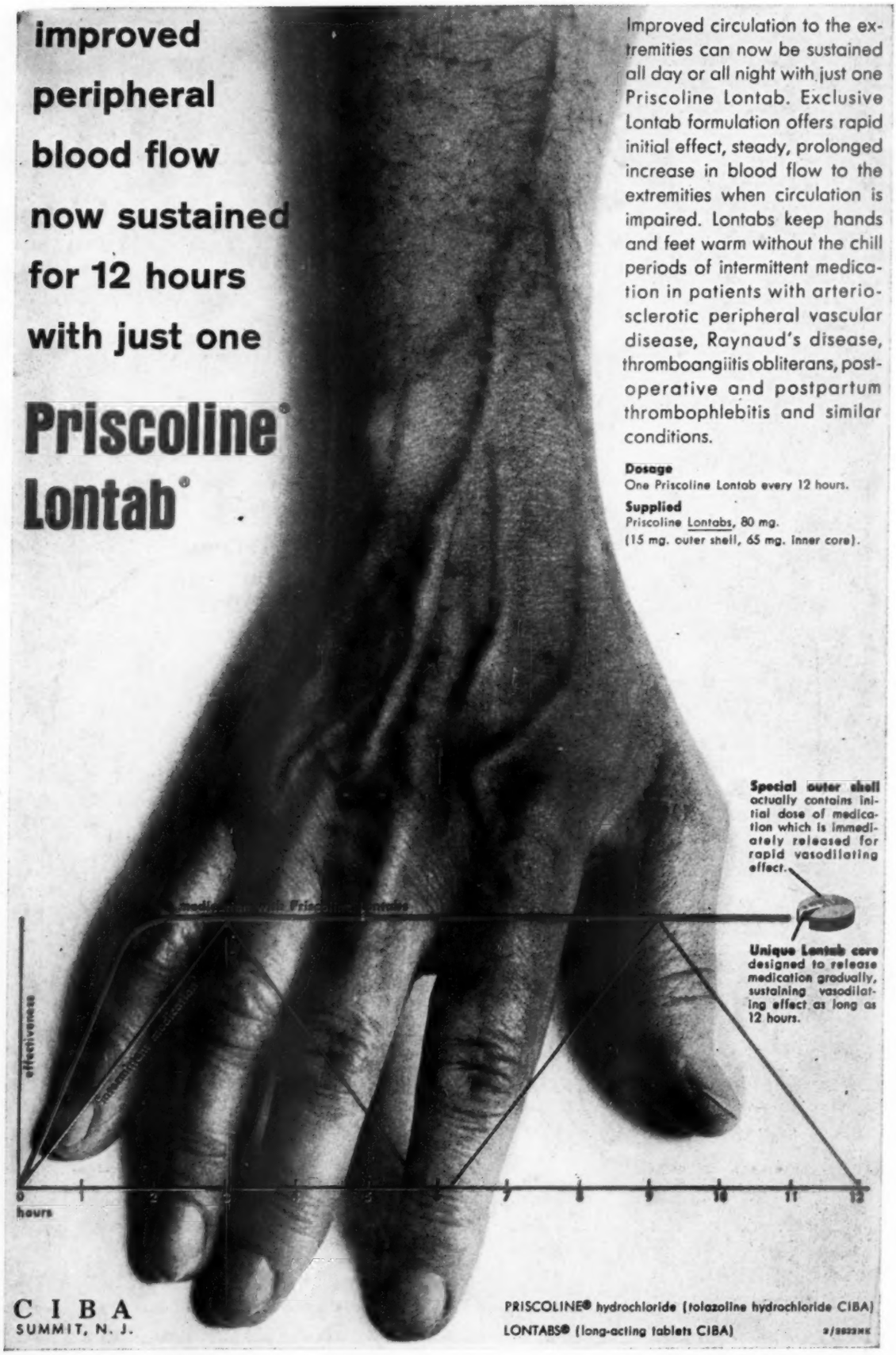
improved peripheral blood flow now sustained for 12 hours with just one

Priscoline® Lontab®

Improved circulation to the extremities can now be sustained all day or all night with just one Priscoline Lontab. Exclusive Lontab formulation offers rapid initial effect, steady, prolonged increase in blood flow to the extremities when circulation is impaired. Lontabs keep hands and feet warm without the chill periods of intermittent medication in patients with arteriosclerotic peripheral vascular disease, Raynaud's disease, thromboangiitis obliterans, postoperative and postpartum thrombophlebitis and similar conditions.

Dosage
One Priscoline Lontab every 12 hours.

Supplied
Priscoline Lontabs, 80 mg.
(15 mg. outer shell, 65 mg. inner core).



CIBA
SUMMIT, N. J.

PRISCOLINE® hydrochloride (tolazoline hydrochloride CIBA)
LONTABS® (long-acting tablets CIBA)